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# An Olefin Cross-Metathesis Approach to Depudecin and Stereoisomeric Analogues

Iván Cheng-Sánchez, Cristina García-Ruiz,[#] Guillermo A. Guerrero-Vásquez and Francisco Sarabia[*]

Department of Organic Chemistry

Faculty of Sciences. University of Malaga.

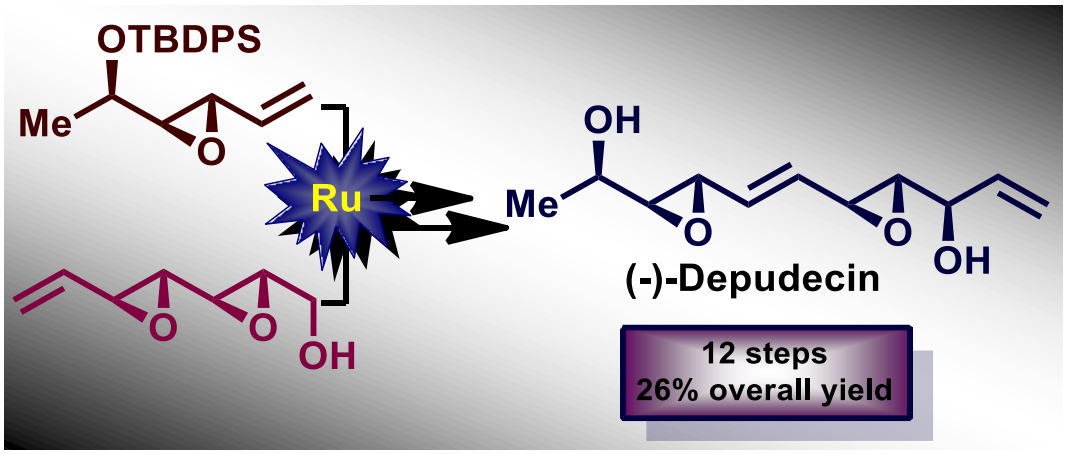
Campus de Teatinos s/n. 29071. Malaga (SPAIN)

Telephone: 34-952 134258. Fax: 34-952 131941

Email: frsarabia@uma.es

# Current address: School of Chemistry, University of Bristol

Cantock´s Close, Bristol BS8 1TS, UK




**Abstract:** A new total synthesis of the natural product (-)-depudecin, a unique and unexplored histone deacetylase (HDAC) inhibitor, is reported. A key feature of the synthesis is the utilization of an olefin cross-metathesis strategy, which provides for an efficient and improved access to natural depudecin, compared with our previous linear synthesis. Featured by its brevity and convergency, our developed synthetic strategy was applied to the preparation of the 10-*epi* derivative and the enantiomer of depudecin, which represent interesting stereoisomeric analogues for structure-activity relationship studies.

## INTRODUCTION

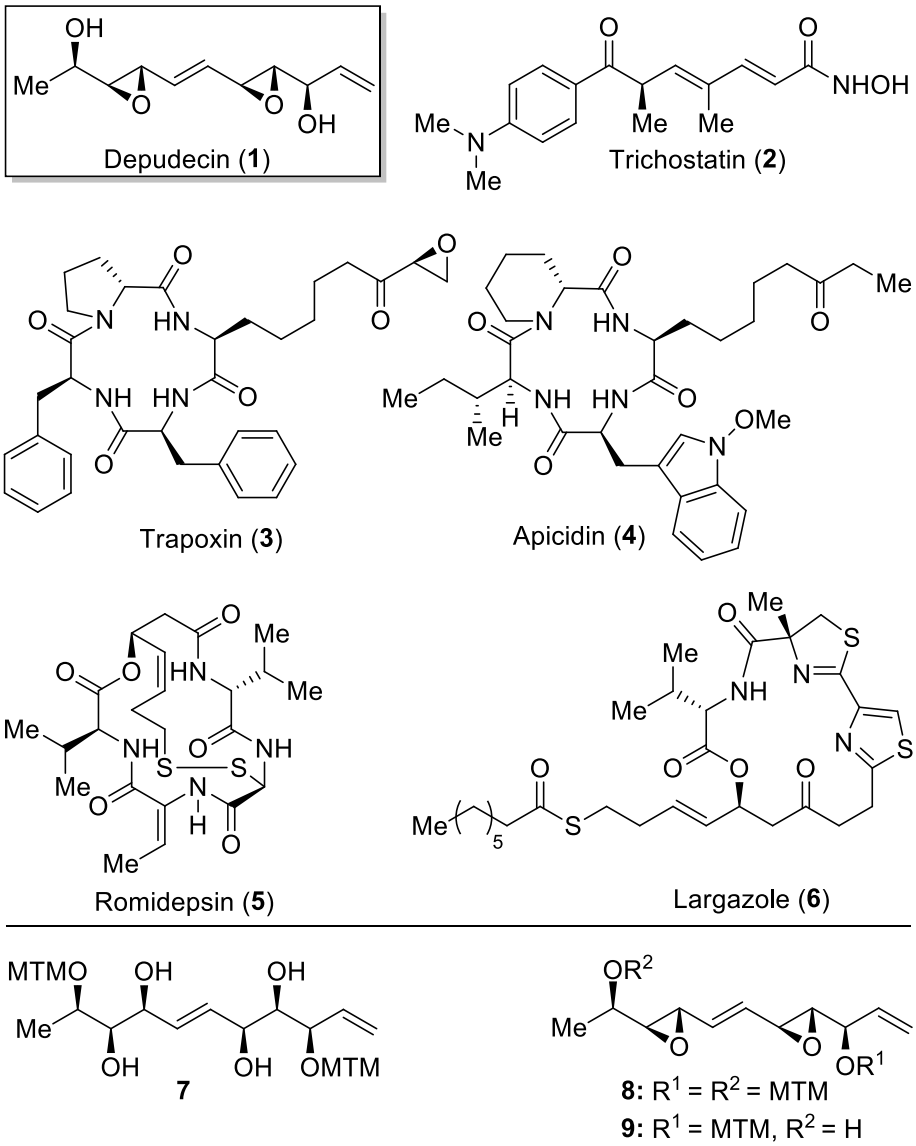
The disclosure and recognition of the crucial role of histone deacetylases (HDAC) and histone acetyl transferases (HAT) in the regulation of gene expression, which occurs through a tight control of the acetylation state of histones, has generated significant interest in their utility as new promising targets for cancer therapies.[1] Thus, whereas the acetylated histones lead to a local expansion of chromatin, increasing the accessibility of regulatory proteins to DNA, the action of HDACs produces positively-charged histones that increase their affinities with DNA and, thereby, block the transcription of anti-tumor genes.[2] HDACs are the enzymes responsible for the removal of the acetyl group from lysine residues of histones and other proteins; and are comprised of 18 isoforms grouped into four different classes (I-IV).[3] The inhibition of these enzymes in the context of a neoplastic epigenome, in which they are overexpressed and play important roles in promoting cancer progression,[4] leads to the restoration of a normal epigenetic state and induces the expression of tumor-suppresive genes.[5] Consequently, inhibitors of HDAC (HDACi) have attracted considerable attention from the scientific community as novel potential anticancer agents.[6] An indication of this interest is the flurry of activity directed towards the design and synthesis of inhibitors, which have been classified into five categories according to their modes of action.[7] As a consequence of this intense activity, three of them (vorinostat, belinostat and romidespin) have been recently approved by the FDA for clinical anticancer therapies, whereas a remarkable number of other HDACi have undergone clinical trials for the treatment of a variety of hematological malignancies and solid tumors.[8] The fact that other proteins, including transcription factors, DNA repair enzymes, signal transduction and inflammation mediators, among others, are also substrates of HDACs, further demonstrates their involvement in a wide variety of biological processes, including cell cycle and mitosis, DNA damage repair, cellular stress responses, protein degradation, cytokine signalling, immunity, inflammation, angiogenesis, apoptosis and cell invasion.[9] In fact, HDACs are involved not

only in cancer, but also in other pathologies such as neurological diseases, immune disorders[10] and infections.[11] On the other hand, the general lack of isoform selectivity exhibited by current inhibitors towards the HDAC family,[12,13] which are involved in a plethora of biological functions, explains the diverse biological effects that they may produce,[14] thus reducing their therapeutic window by promoting undesirable side effects and toxicity.

In this context, (-)-depudecin (**1**), isolated from the culture broths of the fungus *Alternaria brassicicola* in 1992[15] and later, from the weed pathogen *Nimbya scirpicola*,[16] has been identified as a selective inhibitor of histone deacetylases I and II with an $IC_{50}$ in the low μM range, according to biological studies carried out by Schreiber et al.[17] In contrast to representative HDACi, such as **2-6** (Figure 1), depudecin represents a unique inhibitor of these enzymes by virtue of its molecular structure, featuring the presence of two oxirane rings separated by a *trans* double bond.[15] Originally discovered as part of a biological screen directed towards the identification of antitumour agents with detransforming activity,[18] depudecin was identified as a bioactive metabolite capable of reverting the transformed morphology of tumor cells NIH3T3, doubly transfected with v-*ras* and v-*src* oncogenes.[19] The ability of depudecin to regulate the cytoskeletal architecture of tumoral cells is due to the restoration of the actin stress fiber. This biological activity elicited a great biomedical and biological interest[20] by virtue of its potential as an antitumor agent and as a molecular probe[21] for the investigation of signalling pathways that regulate the actin stress fiber, as well as for further understanding the biological roles of HDACs. Depudecin induced not only morphological changes but also cell cycle arrest and cellular differentiation, which could be attributed to its inhibition against HDAC[22] as mentioned above. It is likely that its inhibitory action against HDCA is a result of the presence of biologically reactive oxirane rings that could block the active site of the enzymes through the irreversible formation of a covalent bond between the nucleophlic residues within the active site and the oxirane rings.[23] In fact, Schreiber demonstrated that the epoxy and hydroxyl groups of depudecin were essential for

the biological activity, as the synthetic analogue **9** showed very weak activity, and **7** and **8** were completely inactive against transformed NIH3T3 cells.[24] Furthermore, depudecin also exhibited remarkable anti-angiogenesis activity that endowed it with potent anti-proliferative activity against HUVEC.[25] Finally, in addition to its antitumor properties, depudecin was also identified as a potent anti-protozoal agent against *Neospora caninum*, without any side effects for the host cell.[26]

**Figure 1.** Molecular Structures of (-)-Depudecin (**1**) and Other HDAC Inhibitors

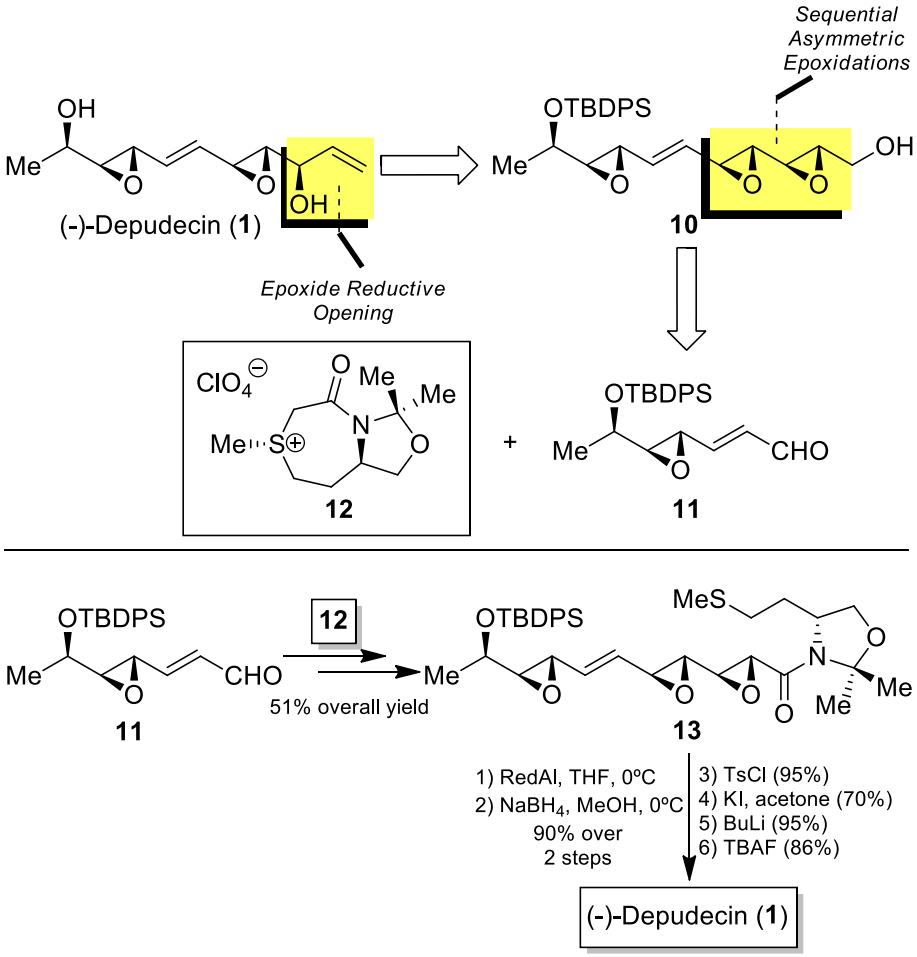


Despite the intriguing biological activities of depudecin and its unique molecular structure, it is rather surprising that only one total synthesis has been reported so far, by the group of Schreiber in 1995.[24] This synthesis was based on an asymmetric methodology that used a one-pot procedure for the stereoselective conversion of *syn*-vicinal diols into *trans*-epoxides, proceeding in 23 steps with an overall yield of 0.7%. Although the synthesis was a long linear synthesis, it was able to provide sufficient amounts of synthetic (-)-depudecin, together with related intermediates (**7**-**9**) for further biological studies.

Prompted by its striking biological properties and enticing structure, we decided to initiate a research program directed towards the synthesis of natural depudecin and analogues. Our synthetic plan has recently culminated with a total synthesis based on the retrosynthetic analysis depicted in Scheme 1.[27] Accordingly, we envisioned triepoxy alcohol **10** as a direct precursor of depudecin via an epoxide reductive elimination process. For the preparation of **10**, we devised the use of a new class of chiral sulfonium salts (**12** and *ent*-**12**), developed in our laboratories,[28,29] for the stereoselective construction of the oxirane rings contained in the natural product. Thus, we prepared triepoxy amide **13** in a remarkable 51% overall yield over 6 steps and with complete stereoselectivity from α,β-unsaturated aldehyde **11**, involving a sequential formation of a diepoxide system mediated by sulfonium salt **12**. From this highly valuable tri-epoxide amide, the completion of the synthesis of depudecin was achieved without problems through triepoxy alcohol **10** (Scheme 1).

In order to develop an improved and expeditious access to natural depudecin, as well as to access additional analogues for further biological screenings, we explored a synthetic alternative based on a olefin cross-metathesis strategy as a shorter and more convergent approach.

**Scheme 1.** Synthesis of (-)-Depudecin: The Linear Approach



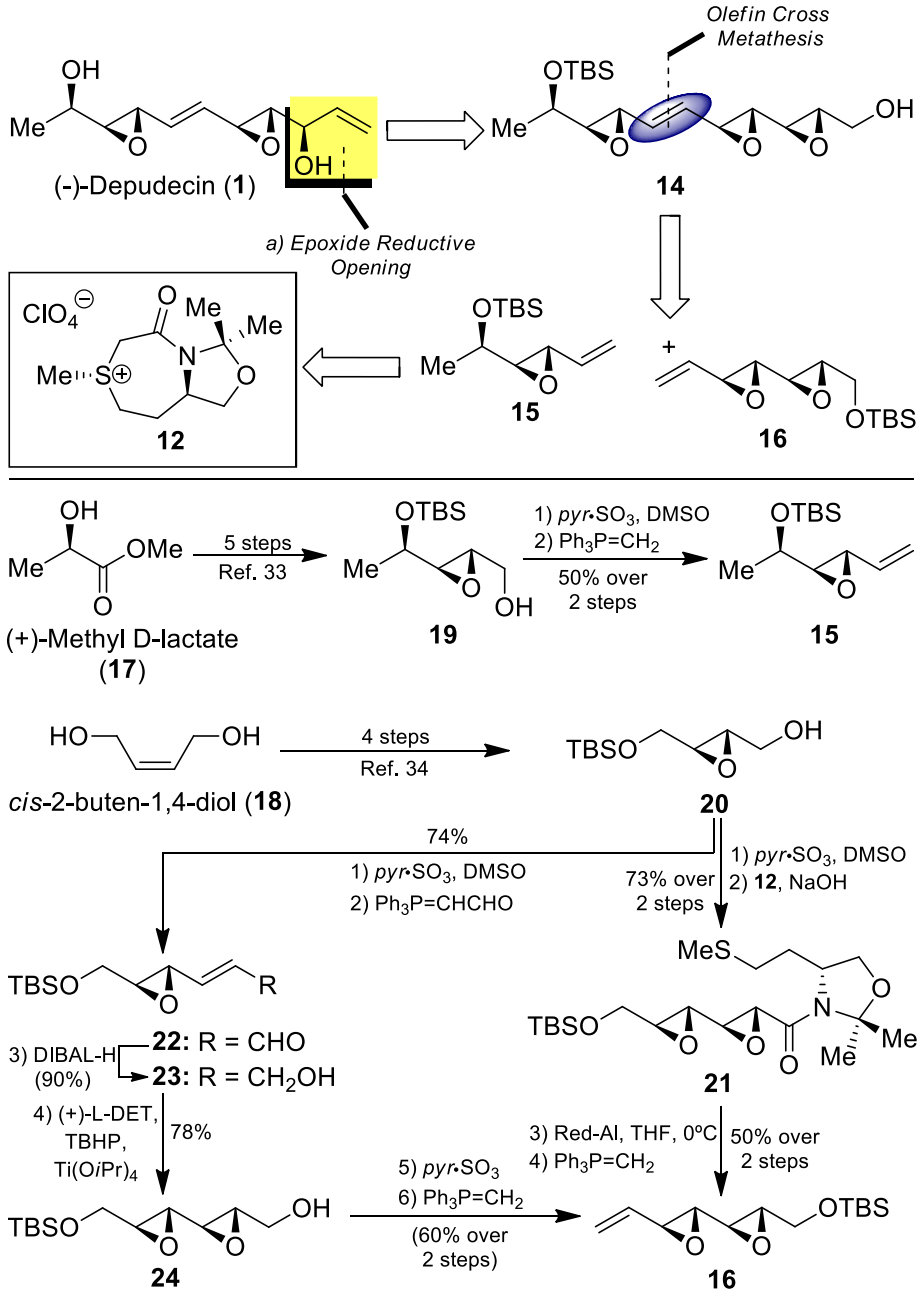

## RESULTS AND DISCUSSION

For the new synthesis of depudecin, we conceived of a convergent approach wherein an olefin cross-metathesis reaction[30] would serve as the key step to join the terminal olefins **15** and **16**. Thus, according to the retrosynthetic analysis depicted in Scheme 2, (-)-depudecin (**1**) could be obtained again from a triepoxy alcohol (**14** in this case) via an epoxide reductive elimination process[31] in the synthetic direction. This triepoxy alcohol **14**, in turn, could be delivered from a key olefin cross-metathesis of compounds **15** and **16**. The preparation of these metathesis precursors was envisioned to be readily feasible from the commercially available (+)-methyl-D-lactate (**17**) and *cis*-2-buten-1,4-diol (**18**), respectively. The synthesis of the required precursors proceeded as shown in Scheme 2. Thus, we begun with the

synthesis of **15** starting from **17**, which was transformed into epoxy alcohol **19** via a Sharpless asymmetric epoxidation (SAE),[32] from the corresponding allylic alcohol.[33] From epoxy alcohol **19**, the synthesis continued by a two step sequence, involving oxidation and Wittig reaction, to obtain **15** in a 50% overall yield. For the other key fragment **16**, we planned to start from the known epoxy alcohol **20**,[34] obtained from *cis*-2-buten-1,4-diol (**18**) in 4 steps. From **20**, the construction of the second oxirane ring was achieved via the sulfonium salt **12** by reacting the aldehyde derived from a Parikh-Doering oxidation of **20**,[35] to obtain diepoxy amide **21** in a remarkable 73% over two steps and complete stereoselectivity.[36] Subsequent reduction of **21** with Red-Al, followed by a Wittig reaction, afforded alkene **16** in 50% yield over 2 steps. Alternatively, diepoxy olefin **16** was also obtained via a Sharpless asymmetric epoxidation (SAE) of allylic alcohol **23**, resulting from the reduction of the α,β-unsaturated aldehyde **22**, to provide diepoxy alcohol **24**, which was transformed into the olefin **16** in 60% yield over two steps (Scheme 2). Comparatively, the overall yields for both synthetic routes are similar (36.5 and 31%, respectively), with the advantage of the sulfonium salt route being shorter than the SAE path.

With both key fragments in hand, we investigated the viability of the cross-metathesis reaction. For the assembly of both epoxy olefin units, a cross-metathesis of alkenes under the influence of the Hoveyda-Grubbs 2$^{nd}$ generation catalyst (HG-II) was initially attempted.[37] The result was the cross-metathesis product **25**, however in a very low yield (15%), and with the homodimerization compound **26**, as the major product (60%). Various reaction conditions and stochiometries of the involved alkenes were evaluated, including second cycles of metathesis, but these failed to improve the yield of the desired product in all cases. Despite the yield of this reaction being variable and generally modest, we were able to access **14** by a selective deprotection step of the primary alcohol, which was accomplished in the presence of TsOH, resulting in the key triepoxy alcohol **14**, in a 50% yield (Scheme 3).

**Scheme 2.** The Convergent Approach to (-)-Depudecin via Olefin Cross-Metathesis: Synthesis of the Precursors

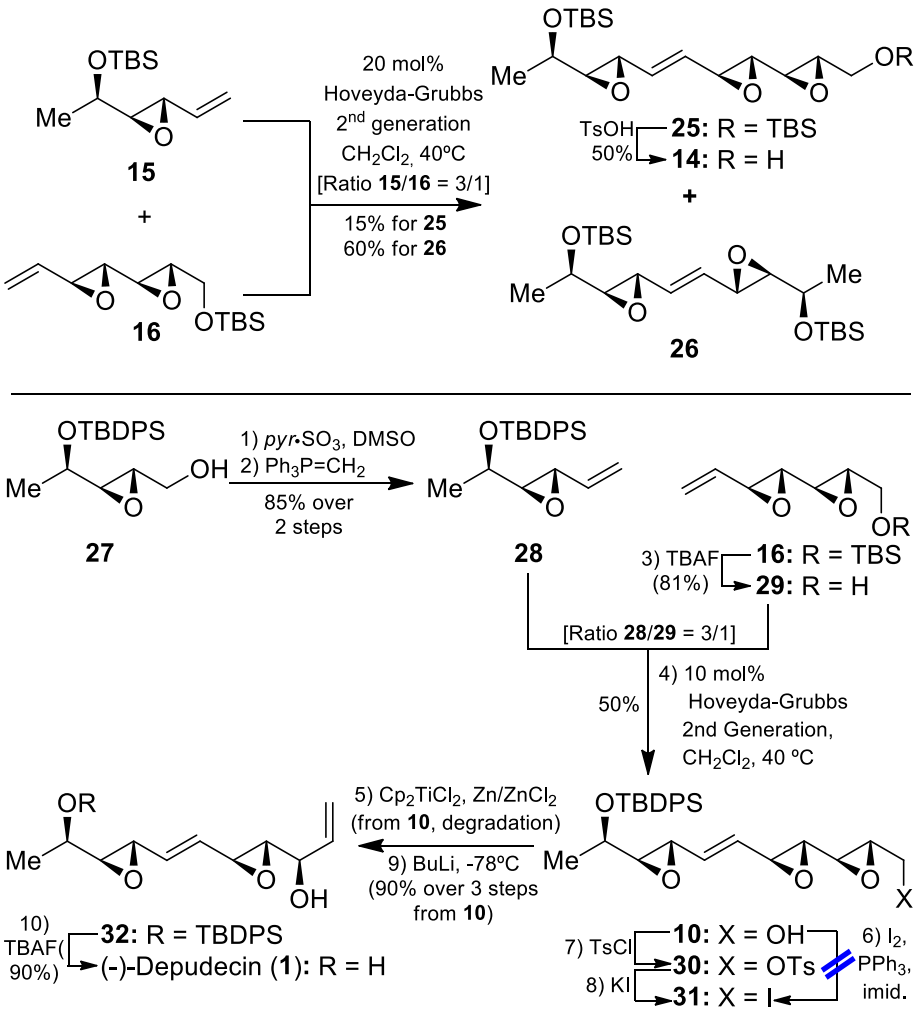



Despite these discouraging results, we decided to press forward with the synthetic strategy by exploring the cross-metathesis from different precursors. To this aim, we reasoned that the placement of a more bulky protected group on the hydroxyl group of the lactate fragment could reduce the dimerization process thus favoring the cross-metathesis reaction. Therefore,

we considered a second attempt with the TBDPS derivative **28**, prepared in the same way as for **15** from the known epoxy alcohol **27**.[27] On the other hand, we decided to use the unprotected diepoxy olefin **29**, as the other metathesis precursor, with the purpose of obtaining a product more closer to depudecin, and without the requirement of additional selective deprotection steps. To our delight, the crucial cross-metathesis reaction between precursors **28** and **29**, in the presence of HG-II catalyst in refluxing dichloromethane, proceeded smoothly to afford the coveted cross-metathesis product **10** in a reasonable and reproducible 50% yield, exclusively as the *E*-isomer, with no detection of the corresponding dimer of **28**. With compound **10** in hand, we proceeded to completion of the synthesis of (-)-depudecin. To this end, we initially attempted a straightforward synthesis of depudecin derivative **32** from triepoxy alcohol **10** through a titanocene-assisted epoxide reductive opening.[38] In this event, triepoxy alcohol **10** was subjected to the combined action of $Cp_2TiCl_2$/Zn. Unfortunately, the result of this reaction was a complex mixture of decomposition products, with none of the desired protected depudecin **32** detected. Similarly discouraging was the attempt of preparing iodide **31** directly from **10** by treatment with iodine/$Ph_3P$ in the presence of imidazole, which also resulted in a complex mixture of degradation products. Given these unsuccessful results in our attempt to shorten the number of steps for the completion of the synthesis of depudecin, we returned to our synthetic sequence employed in our first total synthesis. Fortunately, we were able to improve the yields of the subsequent transformations after optimization of the reaction conditions. Thus, the alcohol **10** was converted into the corresponding alcohol **32**, through tosylation and subsequent displacement of the intermediate tosylate **30** with NaI, to obtain iodide **31**, which was then subjected to treatment with BuLi and no further purification. As a result, the resulting alcohol **32** was obtained in a 90% overall yield over three steps from **10**. The final deprotection step provided natural depudecin (**1**), similarly in an improved yield (90% versus 86% in our first

total synthesis). The physical and spectroscopic properties of synthetic **1** were in accordance to those reported for the natural compound.[15,23]

**Scheme 3.** The Convergent Approach to (-)-Depudecin via Olefin Cross-Metathesis: Completion

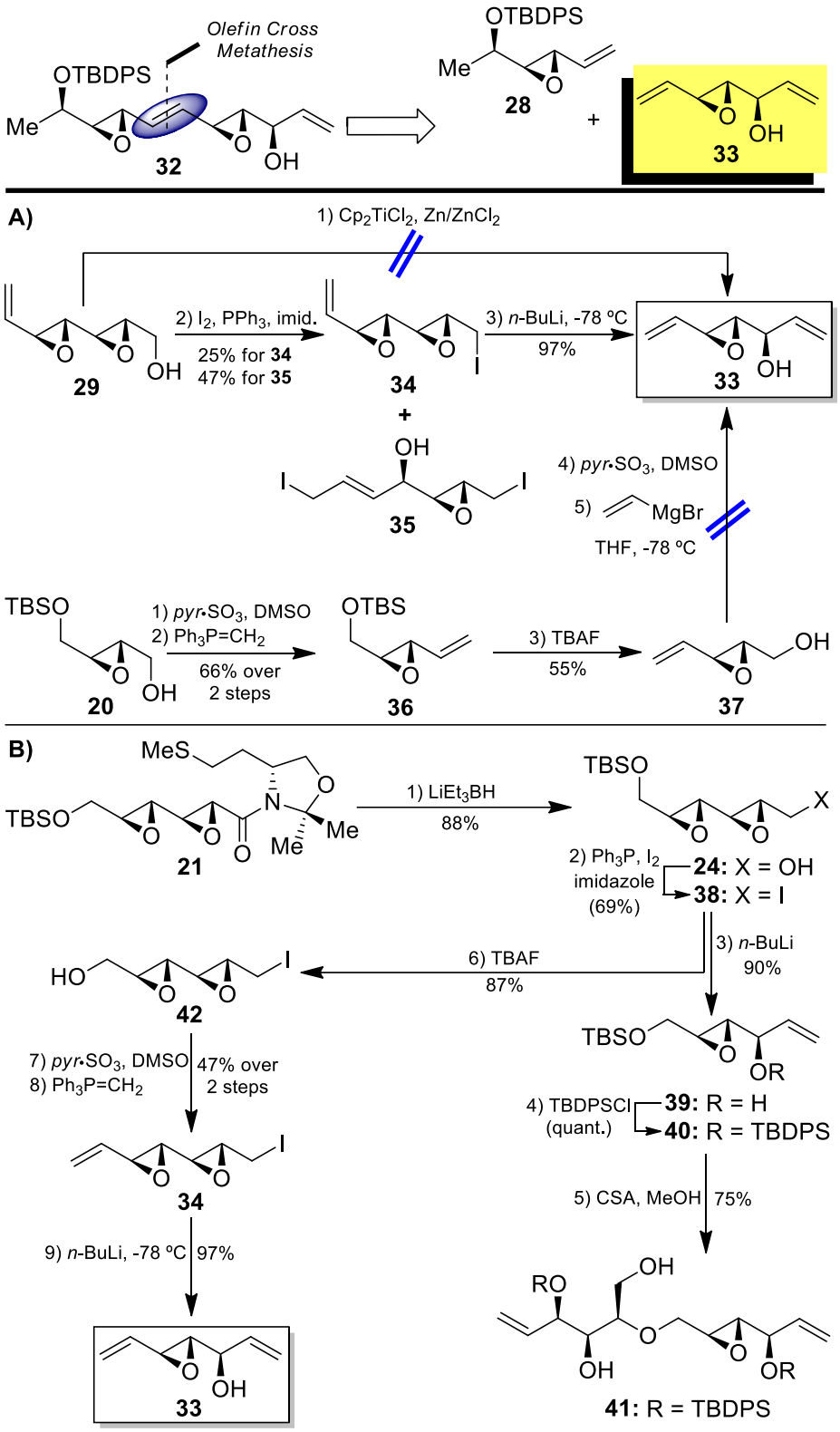



In light of these encouraging results, we devised the possibility of a direct cross-metathesis reaction between olefin **28** and diolefin **33** that would furnish the direct precursor **32** in a single step. It is important to consider that this metathesis reaction is prone to give a mixture of different products, due to the presence of two terminal olefins in **33**. However, a possible coordination involving the allylic alcohol and the catalyst could arrest the catalytic cycle at this terminal olefin to favor the metathesis in the desired direction.[39] To this end, we

proceeded with the synthesis of compound **33**, whose synthesis was more difficult than initially expected, despite its small size. Initially, we attempted the direct reductive opening of diepoxy alcohol **29**, again by the action of a titanocene reducing agent. As in the case for compound **10**, the reaction was completely unsuccessful. Thus, we proceeded with the preparation of iodide **34** by direct iodination of **29** to obtain **34** albeit in a poor yield (25%), due to the formation of the diiodide **35** in a 47% yield, as the main product. Despite this disappointing yield, iodide **34** was subjected to the action of BuLi to provide the targeted diolefin **33**, in almost quantitative yield. Given the poor yield of the iodination step, we attempted the synthesis of this compound via a tosylate derivative. However, the result was similarly disappointing due to competing ring opening reactions of the oxirane with the halides present in the reaction mixture, during both the tosylation, as well as during the nucleophilic iodination step. The low yielding conversion of diepoxy alcohol **29** to the target **33**, through iodide **34**, prompted us to investigate various other synthetic alternatives. Thus, in a second attempt, we prepared epoxy alcohol **37**[40] from **20**, in order to construct the hydroxy allylic system via a vinyl magnesium bromide addition to the resulting aldehyde. However, after oxidation of **37**, the reaction with the Grignad reagent failed to deliver the desired product (Scheme 4, part A). In a third alternative route, we chose to test the approach involving early stage installation of the allylic alcohol system, in order to construct at a later time, the terminal olefin adjacent to the epoxide. Thus, starting from **24**, which was readily obtained from diepoxy amide **21**, compound **39** was efficiently synthesized and then elaborated for the introduction of the other terminal olefin. In particular, after protection of **39** as a TBDPS ether, the selective deprotection of the primary alcohol of the resulting *bis*-silyl ether **40** afforded, unfortunately, compound **41** as a result of the opening of the resulting epoxy alcohol by another epoxy alcohol molecule. Finally, in a fourth attempt, from iodide **38**, we decided to prepare olefin **34** prior to the reductive opening process. Thus, desilylation of iodide **38** was followed by an oxidation step of the resulting alcohol **42**, followed by a Wittig

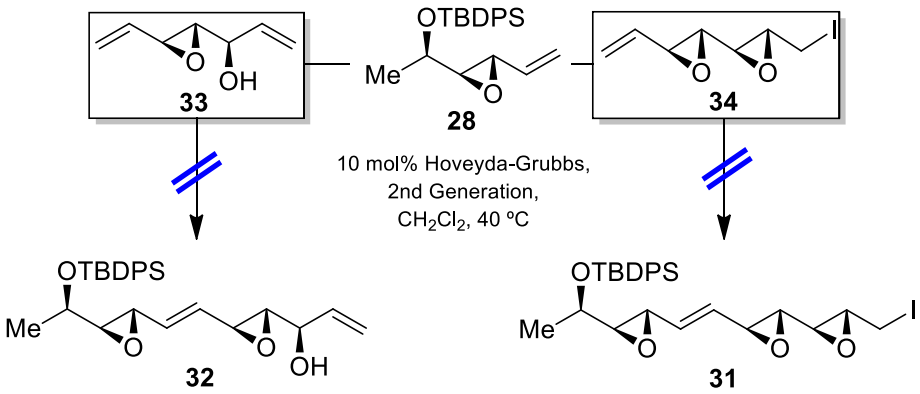
reaction, to afford **34** in a modest 47% overall yield. From iodide **34**, the synthesis of **33** proceeded in a similar manner as described above (Scheme 4, part B).

**Scheme 4.** A Direct Cross-Metathesis Approach to (-)-Depudecin: Synthesis of Precursor **33**



With the diolefin **33** in hand, the cross-metathesis reaction was attempted under the same conditions as previously described for the synthesis of **10**. To our dismay, the reaction was completely unsuccessful, with the formation of a complex mixture of compounds and no detection of any cross-metathesis product, such as the desired **32**. In a modified attempt to obtain additional direct precursor of depudecin, we tried the cross-metathesis of olefins **28** and **34**. Unfortunately, the result was similarly disappointing with no detection of the desired product **31** (Scheme 5).

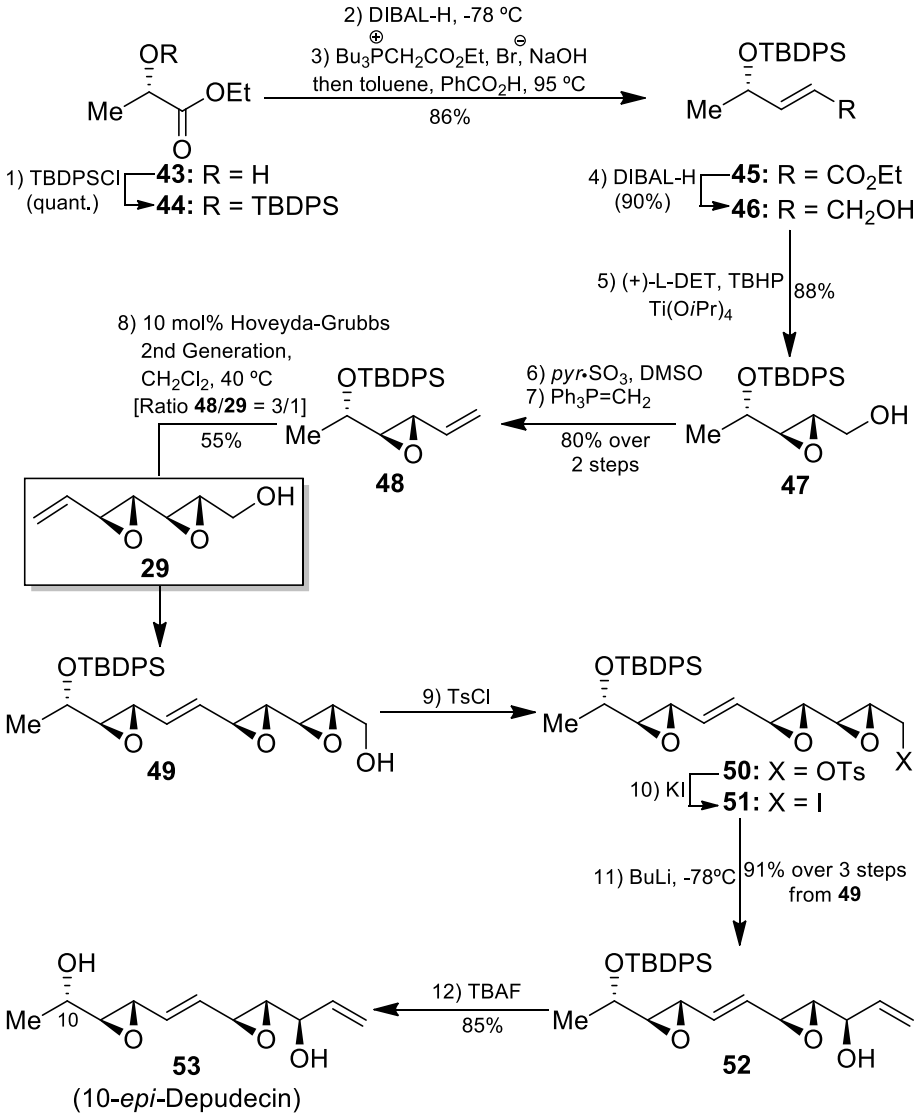
**Scheme 5.** Attempts of the Direct Cross-Metathesis Approach




Due to the previous unsatisfactory results, the direct approach to depudecin was abandoned in favor of the route described in Scheme 3. Having secured a cross-metathesis strategy for this natural product, we decided to pursue depudecin analogues utilizing this methodology. Since the oxirane rings appears to be essential and required for the biological activity of depudecin, we decided to retain these functional groups within the designed analogues, considering therefore depudecin stereoisomers as the most interesting and promising compounds from a biological standpoint. In this sense, we considered as prime candidates the 10-*epi* analogue of depudecin, compound **53**, and the enantiomer, (+)-depudecin (*ent*-**1**), which would be obtained from the readily available (-)-ethyl L-lactate (**43**) as a common starting material. In the case of the 10-*epi* analogue of depudecin, the synthesis of the precursor **48** was carried out

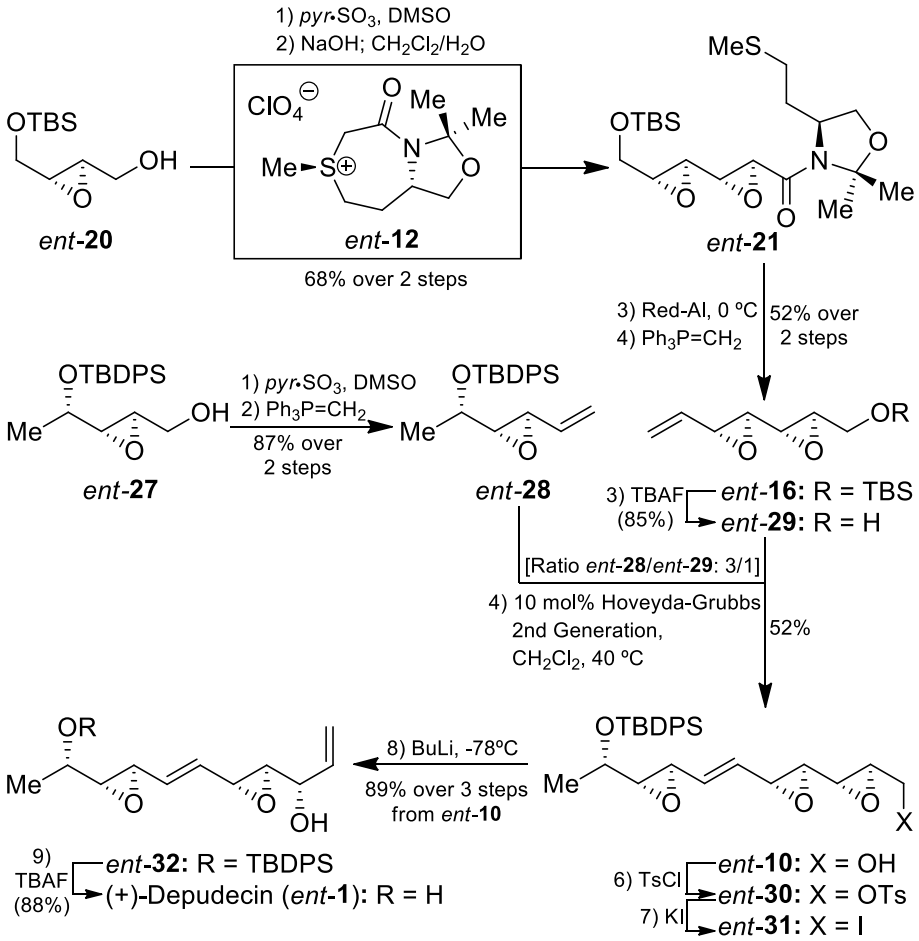
from (-)-ethyl L-lactate (**43**) in an efficient and stereoselective manners (54% yield over 7 steps) via a tandem Wittig-Martin[41]/SAE, according to the sequence depicted in Scheme 6.[42] Then, following on our previously developed strategy to depudecin, we subjected **48** to a cross-metathesis reaction with **29** to afford product **49** in a reasonable 55% yield. From **49**, the completion of the depudecin analogue **53** followed the same synthetic sequence as for (-)-depudecin (**1**) through compounds **50**-**52** and in similar yields (Scheme 6).

**Scheme 6.** Synthesis of 10-*epi*-depudecin (**53**)



Finally, for the synthesis of the enantiomer of depudecin, the compounds *ent*-**28** and *ent*-**29** were prepared without any difficulty via Sharpless asymmetric epoxidation for *ent*-**28**, from the corresponding allylic alcohol **46**, through epoxy alcohol *ent*-**27**,[43] and via chiral sulfonium salt *ent*-**12** for *ent*-**29**. Both olefinic precursors were then joined via a cross-metathesis reaction to afford *ent*-**10** in a 52% yield, which was taken on to (+)-depudecin (*ent*-**1**) as described above for the natural product (Scheme 7).

**Scheme 7.** Synthesis of (+)-depudecin (*ent*-**1**)

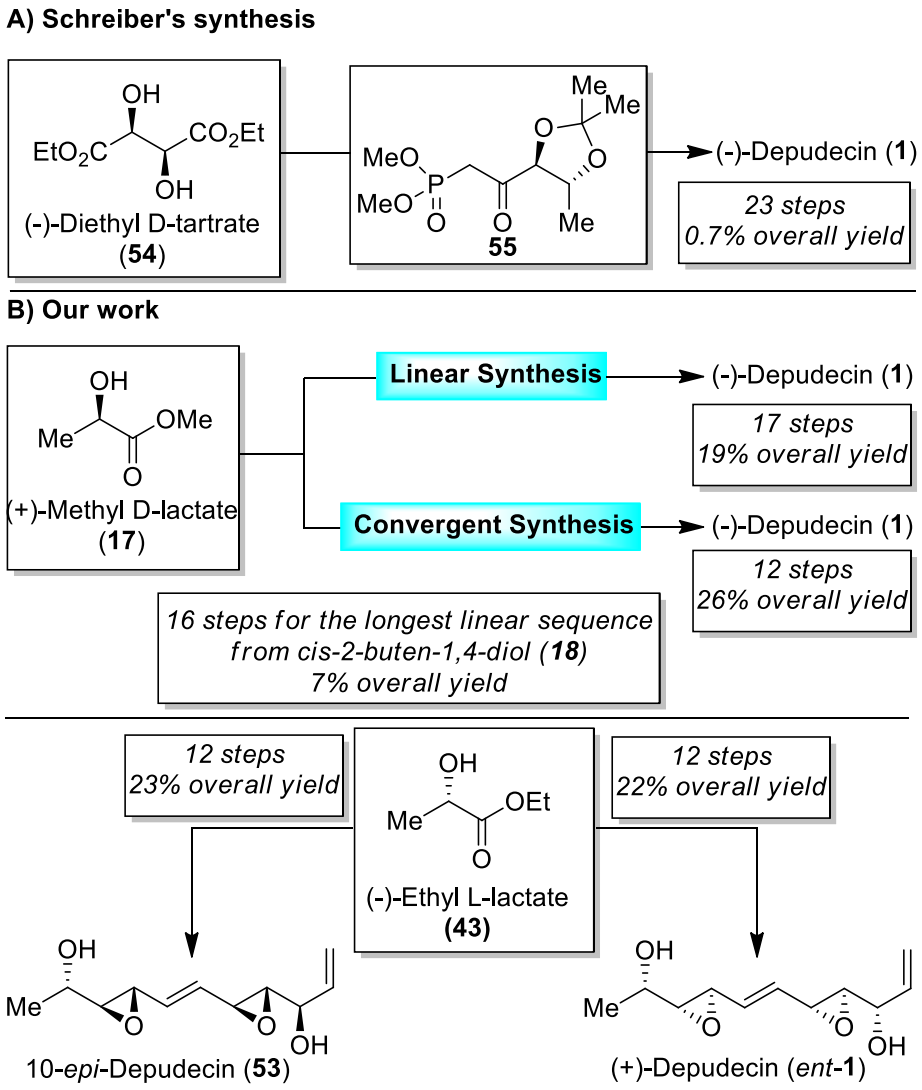



## CONCLUSIONS

In conclusion, we have established a new synthesis of (-)-depudecin **1**, which greatly improves upon our previous linear synthesis. Comparatively, whereas the first total synthesis, reported by Schreiber, required 23 linear steps from (-)-diethyl D-tartrate (**54**), with an overall yield of

0.7%, our first linear synthesis from **17** was achieved in 17 steps in a 19% overall yield (Scheme 8). As continuation of our previous work, we have developed a second generation synthetic route to depudecin utilizing an olefin cross-metathesis reaction as the key step, which was successfully achieved in a convergent manner to provide (-)-depudecin (**1**) in only 12 steps and 26% overall yield from **17**.

**Scheme 8.** Summary of the Syntheses of Depudecin and Analogues




In addition, the synthetic route was amenable to stereochemical modifications, allowing the preparation of two stereoisomers of (-)-depudecin, the 10-*epi*-depudecin and its enantiomer,

which represent unique analogues that will further assist us to evaluate the influence of the stereochemistry upon biological activity. The described chemistry, in addition to rendering (-)-depudecin (**1**) readily available for further biological investigations, also provides rapid access to analogues for structure-activity relationship studies. The biological evaluation of the described compounds, together with other analogues, is currently in progress and will lead us to define their clinical potential for anticancer therapy through their inhibitory activity and isoform specificity against HDACs.

## EXPERIMENTAL SECTION

**General Information.** All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless using aqueous reagents or otherwise noted. All solvents used in reactions were dried and distilled using standard procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone, and dichloromethane ($CH_2Cl_2$) and MeOH from calcium hydride. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. Flash column chromatography (FCC) was performed using silica gel 60 Å (particle size 230-400 mesh) under air pressure. All solvents used for chromatographic purifications were distilled prior to use. All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (60F-254) and visualized by UV light (254 nm) or potassium permanganate or acidic ceric ammonium molybdate/phosphomolybdic acid soluction and heat as developing agents. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX-400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard

($^{13}CDCl_3$: 7.26 ppm, s and 77.0 ppm, t). Data are reported as follows: chemical shift δ/ppm (multiplicity (s = singlet, d = doublet, t = triplet; q, quartet; b = broad, m, multiplet or combinations thereof), coupling constants J (Hz), integration ($^1$H only) and assignment). $^{13}$C signals are singles, unless otherwise stated. High resolution mass spectrometry (HRMS) was performed on a H-ESI and APCI mass spectometer in positive mode and using an ion trap (Orbitrap) as the mass analyzer type. HRMS signals are reported to 4 decimal places and are within ± 5 ppm of theoretical values. Specific optical rotations were recorded on a Jasco P-2000 polarimeter with a sodium halogen lamp (ƛ= 589 nm) and a cell path length of 100 mm (c givn in g/100 mL). Melting points were collected using a Gallenkamp or a Griffin melting point system using a gradient of 0.5ºC per min.

**Epoxy Alkene 15.** A solution of epoxy alcohol **19**[33] (220 mg, 0.95 mmol, 1.0 equiv) in a 1:1 DMSO:$CH_2Cl_2$ mixture (20 mL) was treated with $Et_3N$ (0.4 mL, 14.20 mmol, 3.0 equiv) and $SO_3$·py (375 mg, 2.37 mmol, 2.5 equiv) at 0 ºC. The mixture was stirred until complete conversion of the alcohol (~ 3 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with $Et_2O$. The aqueous phase was extracted with $Et_2O$ twice and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~0.95 mmol) which was used in the next step without further purification. To a stirred suspension of methyl triphenylphosphonium bromide (693 mg, 1.90 mmol, 2.0 equiv) in THF (10 mL) at 0 ºC was added dropwise NaHMDS (0.95 mL, 2.0 M in THF, 1.87 mmol, 2.0 equiv). The resulting suspension was stirred for 30 min at this temperature, and after this time, a solution of the crude aldehyde (~0.95 mmol) in THF (5 mL) was added dropwise, and the resulting mixture stirred for 1 h. After this time, the crude mixture was diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was extracted with $Et_2O$ and the combined organic extracts were washed with brine, dried

over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain epoxy alkene **15** (100 mg, 50% over two steps) as a pale yellow oil: $R_f$ = 0.74 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 35.2 (*c* 0.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.63–5.53 (m, 1 H), 5.45 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.26 (ddd, *J* = 10.2, 1.5, 0.5 Hz, 1 H), 3.66–3.58 (m, 1 H), 3.20 (dd, *J* = 7.5, 2.2 Hz, 1 H), 2.85 (dd, *J* = 5.9, 2.2 Hz, 1 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.5, 118.9, 67.5, 63.5, 56.5, 25.8, 20.8, 18.1, –4.7, –4.9; HRMS (H-ESI) *m/e* calcd for $C_{12}H_{24}O_2Si$ $[M + H]^+$ 229.1624, found 229.1618.

**Diepoxy Amide 21.** Epoxy alcohol **20**[34] (640 mg, 2.96 mmol 1.0 equiv) was dissolved in a $CH_2Cl_2$/DMSO (1:1) mixture (12 mL) and cooled at 0ºC. At this temperature, $Et_3N$ (1.2 mL, 8.88 mmol, 3.0 equiv) was added followed by $SO_3$·Pyr (840 mg, 5.20 mmol, 1.8 equiv). The reaction mixture was allowed to reach room temperature and, after 5 h, was quenched by addition of a buffer solution (pH = 7) and diluted with $Et_2O$. The aqueous phase was extracted with $Et_2O$ (3 x 20 mL) and the combined organic extracts were washed with water and brine, then dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a suspension of sulfonium salt **12**[28,29] (1.0 g, 3.40 mmol, 1.1 equiv) in *t*-BuOH (40 mL) was added a 5.0 M aqueous NaOH solution (0.6 mL, 3.0 mmol, 1.0 equiv) at 25 ºC. After 1 h at this temperature, a solution of crude aldehyde in *t*-BuOH (10 mL) was added and the resulting reaction mixture was stirred overnight. The crude mixture was then diluted with $CH_2Cl_2$ and $H_2O$ and, after decantation, the aqueous phase was extracted with $CH_2Cl_2$ three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy amide **21** (920 mg,

73% over 2 steps) as a pale yellow oil and whose spectroscopic and physical properties matched with those described in the literature:[36] $R_f$ = 0.20 (Silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = −17.1 (*c* 0.34, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 4.27 (ddd, *J* = 8.8, 4.7, 3.5 Hz, 1 H), 3.97 (ddd, *J* = 9.1, 5.2, 1.3 Hz, 1 H), 3.89–3.86 (m, 1 H), 3.85 (d, *J* = 2.0 Hz, 1 H), 3.69 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.54 (d, *J* = 2.0 Hz, 1 H), 3.30 (dd, *J* = 3.4, 2.0 Hz, 1 H), 3.11–3.06 (m, 2 H), 2.59–2.50 (m, 1 H), 2.48–2.39 (m, 1 H), 2.08 (s, 3 H), 2.05–2.00 (m, 1 H), 1.83–1.73 (m, 1 H), 1.59 (s, 3 H), 1.48 (s, 3 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 162.9, 95.9, 67.0, 61.6, 56.3, 55.9, 55.5, 51.7, 51.2, 34.4, 30.6, 26.2, 25.8, 22.9, 18.3, 15.7, –5.4, –5.4; HRMS (H-ESI) *m/e* calcd for $C_{20}H_{37}NO_5SSi$ $[M + H]^+$ 432.2240, found 432.2239.

**Diepoxy Alkene 16.** To a solution of diepoxy amide **21** (95 mg, 0.34 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise Red-Al (0.03 mL, 70% w/v in toluene, 0.09 mmol, 0.5 equiv) at 0 ºC. After 30 min at this temperature, the reaction mixture was quenched by addition of a saturated aqueous $Na^+/K^+$ tartrate solution and diluted with EtOAc. The resulting mixture was vigorously stirred until a clear separation of both oganic and aqueous phases. After separation of both layers, the aqueous phase was extracted with EtOAc and the combined organic extracts washed with $H_2O$ and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a stirred suspension of methyl triphenylphosphonium bromide (123 mg, 0.35 mmol, 1.75 equiv) in THF (1.0 mL) at 0 ºC was added dropwise NaHMDS (0.18 mL, 2.0 M in THF, 0.35 mmol, 1.75 equiv). The resulting suspension was stirred for 15 min at this temperature, and after this time, a solution of the crude aldehyde (~0.20 mmol) in THF (3.0 mL) was added dropwise, and the resulting mixture was stirred for 30 min. After this time, the crude mixture was diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was extracted with $Et_2O$ and the combined

organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain the epoxy alkene **16** (33 mg, 50% over two steps) as a colorless oil: $R_f$ = 0.89 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –20.2 (*c* 0.39, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.59–5.49 (m, 2 H), 5.35–5.30 (m, 1 H), 3.88 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.75 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.36 (dd, *J* = 7.0, 2.1 Hz, 1 H), 3.11 (ddd, *J* = 4.0, 2.8, 2.2 Hz, 1 H), 3.00 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.4, 2.1 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.5, 128.5, 62.1, 57.7, 56.0, 55.9, 53.3, 29.7, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{13}H_{24}O_3Si$ $[M + H]^+$ 257.1573, found 257.1567.

**Aldehyde 22.** To a solution of epoxy alcohol **20** (4.0 g, 18.32 mmol, 1.0 equiv) in a 1:1 DMSO:$CH_2Cl_2$ mixture (36 mL) was added $Et_3N$ (7.7 mL, 54.95 mmol, 3.0 equiv) followed by $SO_3$·py (7.3 g, 45.79 mmol, 2.5 equiv) at 0 ºC. The reaction mixture was stirred at this temperature until depletion of the starting alcohol as judged by TLC (~ 5 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with $Et_2O$. The aqueous phase was extracted with $Et_2O$ (2 x 30 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~18 mmol) which was used in the next step without further purification. To a solution of the crude aldehyde in $CH_2Cl_2$ (95 mL) was added (formylmethylene)triphenylphosphorane (7.0 g, 23.08 mmol, 1.2 equiv) and the mixture was stirred for 12 h. After this time the solvent was removed under reduced pressure and the residue purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aldehyde **22** (3.3 g, 74% over two steps) as a pale yellow oil: $R_f$ = 0.51 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –24.8 (*c* 0.21, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.57 (d, *J* = 7.7 Hz, 1 H), 6.57 (dd, *J* = 15.8, 6.9 Hz, 1 H), 6.40 (ddd, *J* = 15.8, 7.7,

0.6 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.81 (dd, *J* = 12.2, 3.8 Hz, 1 H), 3.55 (dd, *J* = 6.9, 2.0 Hz, 1 H), 3.12 (ddd, *J* = 3.8, 3.0, 2.0 Hz, 1 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.4, 152.3, 133.9, 61.9, 61.5, 53.4, 25.8, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{22}O_3Si$ $[M + H]^+$ 243.1416, found 243.1398.

**Allylic Alcohol 23.** A solution of aldehyde **22** (3.3 g, 13.61 mmol, 1.0 equiv) in $CH_2Cl_2$ (120 mL) was cooled at -78 ºC and treated with DIBAL-H (13.6 mL, 1.0 M in toluene, 13.61 mmol, 1.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous $Na^+/K^+$ tartrate solution and diluted with $CH_2Cl_2$. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain allylic alcohol **23** (3.0 g, 90%) as a yellow oil: $R_f$ = 0.35 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –31.8 (*c* 0.64, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.09 (dt, *J* = 15.7, 5.3 Hz, 1 H), 5.51 (ddt, *J* = 15.6, 7.9, 1.7 Hz, 1 H), 4.19 (td, *J* = 5.7, 1.6 Hz, 2 H), 3.86 (dd, *J* = 12.0, 3.3 Hz, 1 H), 3.73 (dd, *J* = 12.0, 4.4 Hz, 1 H), 3.32 (dd, *J* = 7.9, 2.1 Hz, 1 H), 3.02 (ddd, *J* = 4.4, 3.2, 2.2 Hz, 1 H), 1.39 (t, *J* = 5.9 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 132.5, 128.2, 62.9, 62.8, 60.4, 55.3, 25.9, 18.4, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_3Si$ $[M + H]^+$ 245.1573, found 245.1595.

**Diepoxy Alcohol 24.** To a suspension of titanium tetraisopropoxide (1.27 mL, 4.29 mmol, 0.35 equiv) and 4Å molecular sieves (8.0 g) in $CH_2Cl_2$ (85 mL) was added (+)-L-DET (0.74 mL, 4.29 mmol, 0.35 equiv) at -20 ºC. After 15 min at this temperature, a solution of allylic

alcohol **23** (3.0 g, 12.27 mmol, 1.0 equiv) in $CH_2Cl_2$ (100 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (5.0 mL, 5.5 M solution in decane, 24.55 mmol, 2.0 equiv) at the same temperature. After 12 h at this temperature, the reaction mixture was quenched with $Me_2S$ (4.2 mL, 56.47 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy alcohol **24** (2.49 g, 78%) as a colourless oil: $R_f$ = 0.40 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –22.4 (*c* 0.51, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.98 (ddd, *J* = 12.8, 4.9, 2.3 Hz, 1 H), 3.88 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.75 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.73–3.68 (m, 1 H), 3.17–3.15 (m, 1 H), 3.11 (ddd, *J* = 4.0, 2.9, 2.2 Hz, 1 H), 3.08 (dd, *J* = 4.6, 2.2 Hz, 1 H), 2.98 (dd, *J* = 4.7, 2.2 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 62.5, 62.0, 56.1, 55.8, 53.5, 53.4, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_4Si$ $[M + H]^+$ 261.1522, found 261.1523.

**Diepoxy Alkene 16 from Diepoxy alcohol 24.** Diepoxy alcohol **24** (1.8 g, 6.91 mmol, 1.0 equiv) was converted to diepoxy alkene **16** (1.0 g, 60% over two steps) according to the procedure described above for **15** by sequential treatments with $Et_3N$ (2.9 mL)/$SO_3$·py (2.8 g) and methyl triphenylphosphonium bromide (5.0 g)/NaHMDS (7.0 mL). The spectroscopic properties of the resulting diepoxy alkene were indetical with those exhibited by **16** obtained above from **21**.

**Bis(silyl eher) 25 and Dimer 26. Cross-Metathesis of Olefins 15 and 16.** Hoveyda-Grubbs 2$^{nd}$ generation catalyst (16 mg, 0.02 mmol, 0.2 equiv), diepoxy alkene **16** (23 mg, 0.09 mmol, 1.0 equiv) and epoxy alkene **15** (60 mg, 0.27 mmol, 3.0 equiv) were dissolved in degassed $CH_2Cl_2$ (8 mL) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by

flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain dimer **26** (23 mg, 60%) and bis(silyl ether) **25** (6 mg, 15%) as a colourless and a pale yellow oils, respectively. **[25]:** $R_f$ = 0.57 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = –31.4 (*c* 0.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.72 (dd, *J* = 15.7, 7.0 Hz, 1 H), 5.64 (dd, *J* = 15.6, 7.0 Hz, 1 H), 3.88 (dd, *J* = 12.2, 2.7 Hz, 1 H), 3.74 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.67–3.60 (m, 1 H), 3.37 (dd, *J* = 7.0, 2.1 Hz, 1 H), 3.23 (dd, *J* = 6.9, 2.1 Hz, 1 H), 3.11–3.07 (m, 1 H), 3.00 (dd, *J* = 4.2, 2.2 Hz, 1 H), 2.93 (dd, *J* = 4.2, 2.1 Hz, 1 H), 2.86 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 132.7, 130.8, 69.2, 64.7, 61.9, 58.1, 56.1, 54.8, 54.8, 53.0, 25.8, 20.3, 18.3, 18.2, –4.8, –5.4; HRMS (APCI) *m/e* calcd for $C_{23}H_{44}O_5Si_2$ $[M + Na]^+$ 479.2625, found 479.2621; **[26]:** $R_f$ = 0.77 (silica gel, 10% EtOAc in hexanes); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.68 (dd, *J* = 4.4, 2.4 Hz, 2 H), 3.77 (dd, *J* = 6.2, 4.3 Hz, 2 H), 3.31 (dt, *J* = 4.4, 2.2 Hz, 2 H), 2.78 (dd, *J* = 4.2, 2.1 Hz, 2 H), 1.23 (d, *J* = 6.3 Hz, 6 H), 0.88 (s, 18 H), 0.05 (s, 6 H), 0.04 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 131.7, 67.2, 63.9, 55.1, 25.8, 20.8, 18.1, –4.7, –4.8; HRMS (APCI) *m/e* calcd for $C_{22}H_{44}O_4Si_2$ $[M + H]^+$ 429.2856, found 429.2862.

**Epoxy Alcohol 14.** Silyl derivative **25** (30 mg, 0.07 mmol, 1.0 equiv) was dissolved in a mixture THF-$H_2O$ (20:1) (5 mL) and over this solution was added *p*-TsOH (2 mg, 0.01 mmol, 0.1 equiv) at 25 ºC. After stirring for 40 min at the same temperature, the solvent was removed under vacuum and the crude mixture purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain diepoxy alcohol **14** (11 mg, 50%) as a pale colourless oil: $R_f$ = 0.38 (Silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –35.2 (*c* 0.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.73 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.64 (dd, *J* = 15.7, 7.2 Hz, 1 H), 3.72 (dd, *J* = 13.2, 3.1 Hz, 1 H), 3.67–3.59 (m, 1 H), 3.39 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.24 (dd, *J* = 7.1, 2.0 Hz, 1 H), 3.19–3.15 (m, 1 H), 3.10 (dd, *J* = 4.3, 2.2 Hz, 1 H), 3.05–3.01 (m, 1 H), 2.94 (dd, *J* = 4.3, 2.1 Hz, 1 H), 2.87 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.60 (bs, 1 H), 1.20 (d, *J* =

6.4 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 132.8, 130.5, 69.1, 64.7, 61.7, 60.4, 57.9, 55.7, 54.8, 53.0, 25.8, 20.3, 18.2, –4.7, –4.8; HRMS (APCI) *m/e* calcd for $C_{17}H_{30}O_5Si$ $[M + H]^+$ 343.1941, found 343.1936.

**Epoxy Alkene 28.** Epoxy olefin **28** was prepared from epoxy alcohol **27**[27] (2.7 g, 7.57 mmol, 1.0 equiv) by sequential treatments with $SO_3$·py and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **15**, to obtain epoxy alkene **28** (2.2 g, 85% over two steps) as a colourless oil: $R_f$ = 0.66 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 12.7 (*c* 0.59, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72–7.68 (m, 4 H), 7.44–7.36 (m, 6 H), 5.56 (ddd, *J* = 17.3, 10.2, 7.7 Hz, 1 H), 5.44–5.38 (m, 1 H), 5.25 (ddd, *J* = 10.3, 1.5, 0.5 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.19 (dd, *J* = 7.7, 2.2 Hz, 1 H), 2.96 (dd, *J* = 5.7, 2.2 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 135.3, 134.3, 133.7, 129.7, 129.6, 127.6, 127.5, 119.3, 69.9, 64.3, 56.1, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1933.

**Diepoxy Alkene 29.** To a solution of silyl ether **16** (700 mg, 2.73 mmol, 1.0 equiv) in THF (70 mL) was added TBAF (5.5 mL, 1.0 M in THF, 5.45 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1 h and, after this time, diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was then extracted with $Et_2O$ twice and the organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes → 30% EtOAc in hexanes) to obtain diepoxy alkene **29** (314 mg, 81%) as a colourless oil: $R_f$ = 0.33 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.8 (*c* 0.27, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.47–5.37 (m, 2 H), 5.24–5.18 (m, 1 H), 3.79 (ddd, *J* = 11.4, 9.0, 2.5 Hz, 1 H), 3.53 (dd, *J* = 12.9, 4.3 Hz, 1 H), 3.29–3.25 (m, 1 H), 3.05 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95–2.90 (m, 1 H), 2.81 (dd, *J* = 4.8, 2.1

Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.2, 120.4, 60.7, 57.9, 56.0, 55.9, 53.5; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_3$ $[M + H]^+$ 143.0708, found 143.0696.

**Triepoxy Alcohol 10. Cross-Metathesis of Olefins 28 and 29.** Hoveyda-Grubbs 2$^{nd}$ generation catalyst (35 mg, 0.06 mmol, 0.10 equiv), diepoxy alkene **29** (80 mg, 0.56 mmol, 1.0 equiv) and epoxy alkene **28** (595 mg, 1.69 mmol, 3.0 equiv) were dissolved in degassed $CH_2Cl_2$ (6 mL) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain triepoxy alcohol **10** (129 mg, 50%) as a colourless oil: $R_f$ = 0.51 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –30.3 (*c* 0.45, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.57 (dd, *J* = 15.6, 7.3 Hz, 1 H), 3.98 (dd, *J* = 10.7, 2.2 Hz, 1 H), 3.76–3.68 (m, 2 H), 3.37 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.21–3.16 (m, 2 H), 3.11 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.94 (ddd, *J* = 6.4, 4.9, 2.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.8, 134.2, 133.6, 132.8, 130.5, 129.7, 127.6, 127.6, 69.7, 64.6, 62.5, 60.4, 57.9, 55.7, 54.7, 52.9, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2073, found 489.2073.

**Tosyl Derivative 30.** Triepoxy alcohol **10** (57 mg, 0.12 mmol, 1.0 equiv) was dissolved in $CH_2Cl_2$ (7 mL) and cooled at 0 ºC. Over this solution was then added *p*-TsCl (28 mg, 0.15 mmol, 1.2 equiv), TEA (30 μL, 0.18 mmol, 1.5 equiv) and 4-DMAP (0.3 mg, 0.002 mmol, 0.02 equiv). After 3 h, the reaction mixture was quenched by addition of water and the aqueous phase was extracted with $CH_2Cl_2$ three times. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to obtain tosyl derivative **30** (90 mg, ~0.12 mmol), which did not require further purification for the

next step. For analytical purposes, a sample of this crude (5.0 mg, ~0.007 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **30** (3.8 mg, 87%) as a colourless oil: $R_f$ = 0.33 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –18.6 (*c* 0.25, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81–7.78 (m, 2 H), 7.71–7.65 (m, 4 H), 7.43–7.34 (m, 8 H), 5.67 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.54 (dd, *J* = 15.6, 7.6 Hz, 1 H), 4.20 (dd, *J* = 11.6, 3.7 Hz, 1 H), 4.08 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.9 Hz, 1 H), 3.22–3.17 (m, 2 H), 2.98 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.94 (dd, *J* = 5.5, 2.2 Hz, 1 H), 2.88 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 145.3, 135.9, 135.8, 134.2, 134.1, 133.6, 133.1, 130.2, 130.0, 129.7, 129.6, 127.9, 127.6, 127.5, 69.7, 68.5, 64.6, 57.1, 54.8, 54.6, 53.8, 52.3, 26.9, 21.7, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2161.

**Iodide Derivative 31.** To a solution of crude tosyl derivative **30** (~85 mg, ~0.11 mmol, 1.0 equiv) in dry acetone (7 mL) was added dry KI (28 mg, 0.17 mmol, 1.5 equiv) at room temperature, and the resulting crude mixture was refluxed for 5.5 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The resulting crude was diluted with $H_2O$ and extracted with $Et_2O$. After separation of both phases, the organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to obtain iodide derivative **31** (80 mg, ~0.11 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (4.5 mg, ~0.006 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford the iodide derivative **31** (3.2 mg, 93%) as a colourless oil: $R_f$ = 0.56 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= –19.4 (*c* 0.45 $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71–7.66 (m, 4 H), 7.44–7.34 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.56 (dd, *J* = 15.7, 7.4 Hz, 1 H), 3.76–3.69 (m, 1 H), 3.35 (d, *J* = 7.2 Hz, 1 H), 3.28–

3.21 (m, 2 H), 3.20 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.10 (dd, *J* = 12.4, 8.8 Hz, 1 H), 2.96–2.93 (m, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 134.2, 133.6, 132.9, 130.3, 129.7, 129.6, 127.6, 127.5, 69.7, 64.6, 59.4, 57.3, 55.7, 54.8, 54.6, 26.9, 19.9, 19.3, 3.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + Na]^+$ 599.1091, found 599.1088.

**Allylic Alcohol 32.** To a solution of the crude iodide derivative **31** (~80 mg, ~0.10 mmol, 1.0 equiv) in THF (10 mL) was added *n*-BuLi (0.13 mL, 1.6 M in hexane, 0.20 mmol, 2.0 equiv) at -78 ºC, and the reaction mixture was stirred for 5 min. After this time, the reaction mixture was then quenched at -78 ºC with MeOH followed by addition of a saturated aqueous $NH_4Cl$ solution at 0 ºC. The resulting mixture was extracted with EtOAc (3 x 10 mL) and the organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was then removed under reduced pressure and the resulting crude mixture purified by flash column chromatogaphy (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **32** (41 mg, 90% over 3 steps from **10**) as a colourless oil: $R_f$ = 0.57 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –20.9 (*c* 0.28, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71–7.66 (m, 4 H), 7.43–7.34 (m, 6 H), 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.67 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.58 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.40 (dt, *J* = 17.3, 1.3 Hz , 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.15–4.09 (m, 1 H), 3.76–3.70 (m, 1 H), 3.40 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.20 (dd, *J* = 7.0, 2.1 Hz, 1 H), 2.99 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.2, 135.9, 135.8, 134.2, 133.6, 132.7, 130.9, 129.7, 129.6, 127.6, 127.5, 117.0, 71.5, 69.7, 64.5, 62.4, 55.0, 54.8, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2301.

**(-)-Depudecin (1).** Silyl derivative **32** (11 mg, 0.02 mmol, 1.0 equiv) was dissolved in THF (3 mL) and over this solution was added TBAF (29 µL, 1.0 M in THF, 0.03 mmol, 1.2 equiv) at

25 ºC. After 90 min, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was then extracted with EtOAc and the organic extracts were washed with $H_2O$, brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 60% EtOAc in hexanes) to afford (-)-Depudecin (**1**) (4.5 mg, 90%) as a colourless oil: $R_f$ = 0.52 (silica gel, EtOAc); $[\alpha]^{25}_D$= –31.1 (*c* 0.17, $CH_2Cl_2$) (*lit.*[15] $[\alpha]^{24}_D$= –35.8 (*c* 0.52, MeOH); (*lit.*[24] $[\alpha]^{23}_D$= –31.0 (*c* 0.08, $CHCl_3$); (*lit.*[27] $[\alpha]^{25}_D$= –29.6 (*c* 0.12, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.72–5.69 (m, 2 H), 5.40 (dt, *J* = 17.3, 1.3 Hz, 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (d, *J* = 4.4 Hz, 1 H), 3.74 (dd, *J* = 11.3, 6.2 Hz, 1 H), 3.45–3.42 (m, 1 H), 3.40–3.36 (m, 1 H), 3.01 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.91 (dd, *J* = 4.5, 2.2 Hz, 1 H), 1.93 (d, *J* = 6.5 Hz, 1 H), 1.80 (d, *J* = 6.1 Hz, 1 H), 1.31 (d, *J* = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.0, 131.5, 117.1, 71.5, 66.9, 64.1, 62.4, 55.3, 54.9, 20.0; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1115.

**Diepoxy Iodide 34 and Diiodide 35. Iodination of Diepoxy Alcohol 29.** To a solution of diepoxy alcohol **29** (50 mg, 0.35 mmol, 1.0 equiv) in THF (10 mL) at 0 ºC was added imidazole (72 mg, 1.05 mmol, 3.0 equiv), $PPh_3$ (138 mg, 0.53 mmol, 1.5 equiv) and iodine (134 mg, 0.53 mmol, 1.5 equiv) at 25 ºC. The mixture was vigorously stirred at 25 ºC for 20 min. After this time, the solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes→10% EtOAc in hexanes) to obtain diepoxy iodide **34** (22 mg, 25%) and diiodide **35** (42 mg, 47%) as yellow oils. **[34]**: $R_f$ = 0.90 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –35.8 (*c* 0.87, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.58–5.53 (m, 2 H), 5.35–5.31 (m, 1 H), 3.37–3.32 (m, 1 H), 3.28–3.22 (m, 2 H), 3.12–3.05 (m, 1 H), 2.96–2.94 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.1, 120.5, 60.1, 59.6, 57.1, 55.6, 3.2; HRMS (H-ESI) *m/z* calcd for $C_7H_9IO_2$ [M

+ H]$^+$ 252.9726, found 252.9698. **[35]**: $R_f$ = 0.81 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –29.4 (*c* 0.31, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.09 (dtd, *J* = 15.4, 7.9, 1.4 Hz, 1 H), 5.76 (ddt, *J* = 15.2, 5.7, 1.0 Hz, 1 H), 4.09 (dd, *J* = 10.2, 4.9 Hz, 1 H), 3.90–3.86 (m, 2 H), 3.29–3.24 (m, 2 H), 3.10–3.06 (m, 1 H), 2.94 (dd, *J* = 4.6, 1.9 Hz, 1 H), 2.23 (d, *J* = 6.0 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 131.0, 130.8, 70.3, 64.0, 55.9, 3.7, 3.4; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}I_2O_2$ [M + H]$^+$ 380.8848, found 380.8856.

**Dialkene 33.** To a solution of iodide derivative **34** (13 mg, 0.04 mmol, 1.0 equiv) in THF (3 mL) was added *n*-BuLi (50.0 µL, 1.6 M in hexane, 0.08 mmol, 2.0 equiv) at -78 ºC, and the reaction was stirred for 5 min. The reaction mixture was then quenched at -78 ºC with MeOH followed by addition of a saturated aqueous $NH_4Cl$ solution at 0 ºC. The resulting mixture was extracted with EtOAc and the organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was then removed under reduced pressure and the resulting crude mixture purified by flash column chromatogaphy (silica gel, 25% EtOAc in hexanes) to obtain dialkene **33** (6.3 mg, 97%) as a colourless oil: $R_f$ = 0.51 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –12.35 (*c* 0.15, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.95 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.58 (dd, *J* = 9.9, 7.3 Hz, 1 H), 5.53 (d, *J* = 1.8 Hz, 1 H), 5.40 (dt, *J* = 17.3, 1.4 Hz, 1 H), 5.34–5.30 (m, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (t, *J* = 4.7 Hz, 1 H), 3.41 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.00 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.01 (bs, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.3, 134.5, 120.2, 116.9, 71.6, 62.2, 56.3; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_2$ [M + H]$^+$ 127.0759, found 127.0780.

**Epoxy Alkene 36.** Epoxy olefin **36** was prepared from epoxy alcohol **20** (700 mg, 3.21 mmol, 1.0 equiv) by sequential treatments with $SO_3$·py and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **15**, to obtain epoxy alkene **36** (424 mg, 66% over two steps) as a colourless oil: $R_f$ = 0.67 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$= –

29.2 (*c* 0.56, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.64–5.55 (m, 1 H), 5.47 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.27 (ddd, *J* = 10.2, 1.6, 0.6 Hz, 1 H), 3.86 (dd, *J* = 12.0, 3.2 Hz, 1 H), 3.71 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.27 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.99 (ddd, *J* = 4.5, 3.2, 2.2 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.2, 119.4, 62.96, 60.3, 56.1, 25.9, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{22}O_2Si$ $[M + H]^+$ 215.1467, found 215.1465.

**Epoxy Alcohol 37.** Silyl ether **36** (424 mg, 1.98 mmol, 1.0 equiv) was dissolved in THF (40 mL) and to this solution was added TBAF (4.0 mL, 1.0 M in THF, 3.96 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1 h and, after this time, the reaction mixture was diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was then extracted with $Et_2O$ and the organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy alcohol **37** (108 mg, 55%) as a colourless oil: $R_f$ = 0.27 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –19.8 (*c* 0.31, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.60 (ddd, *J* = 17.3, 10.0, 7.4 Hz, 1 H), 5.50 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.31 (dd, *J* = 10.4, 1.7 Hz, 1 H), 3.95 (d, *J* = 12.7 Hz, 1 H), 3.68 (d, *J* = 12.6 Hz, 1 H), 3.40 (dd, *J* = 7.4, 2.2 Hz, 1 H), 3.08 (dt, *J* = 4.1, 2.4 Hz, 1 H), 2.01 (bs, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.7, 120.0, 61.2, 59.9, 55.8; HRMS (H-ESI) *m/z* calcd for $C_5H_8O_2$ $[M + H]^+$ 101.0603, found 101.0597.

**Diepoxy Alcohol 24. Reduction of Diepoxy Amide 21.** Diepoxy amide **21** (700 mg, 1.62 mmol, 1.0 equiv) in THF (30 mL) was treated with $LiEt_3BH$ (3.2 mL, 3.20 mmol, 1.0 M in THF, 2.0 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was separated, extracted with $Et_2O$ twice and the combined organic layers washed with water and brine, dried

over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided diepoxy alcohol **24** (371 mg, 88%) whose physical and spectroscopic properties were identical to those obtained from **23**.

**Iodide Derivative 38.** To a solution of diepoxy alcohol **24** (200 mg, 0.768 mmol, 1.0 equiv) in THF (20 mL) at 0 ºC was added imidazole (157 mg, 2.30 mmol, 3.0 equiv), $PPh_3$ (302 mg, 1.15 mmol, 1.5 equiv) and iodine (292 mg, 1.15 mmol, 1.5 equiv) at 25 ºC. The mixture was vigorously stirred at 25 ºC for 20 min. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain iodide derivative **38** (196 mg, 69%) as a pale yellow oil: $R_f$ = 0.68 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_{D}$ = –24.2 (*c* 0.62, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.88 (dd, *J* = 12.2, 2.7 Hz, 1 H), 3.77–3.71 (m, 1 H), 3.29–3.21 (m, 2 H), 3.15–3.06 (m, 2 H), 3.00 (dd, *J* = 4.2, 2.1 Hz, 1 H), 2.92 (dd, *J* = 4.3, 1.7 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 61.9, 59.9, 56.1, 55.7, 52.8, 25.9, 18.4, 3.5, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{23}IO_3Si$ $[M + H]^+$ 371.0539, found 371.0540.

**Allylic Alcohol 39.** A solution of diepoxy iodide **38** (196 mg, 0.53 mmol, 1.0 equiv) in THF (40 mL) was reacted with *n*-BuLi (0.7 mL, 1.6 M in hexane, 1.06 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **32**, to afford, after similar processing, allylic alcohol **39** (116 mg, 90%) as a colourless oil: $R_f$ = 0.47 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_{D}$= –33.1 (*c* 0.87, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.95–5.78 (m, 1 H), 5.36 (ddd, *J* = 17.3, 1.7, 1.2 Hz, 1 H), 5.22 (ddd, *J* = 10.6, 1.2, 0.7 Hz, 1 H), 4.08–4.01 (m, 1 H), 3.84 (ddd, *J* = 12.2, 3.0, 1.6 Hz, 1 H), 3.67 (tdd, *J* = 4.6, 3.8, 1.1 Hz, 1 H), 3.10 (ddd, *J* = 4.6, 2.0, 0.8 Hz, 1 H), 3.00–2.97 (m, 1 H), 2.41 (bs, 1 H), 0.87 (s, 9 H), 0.05 (s,

3 H), 0.05 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.4, 116.7, 71.9, 62.7, 58.2, 56.4, 25.8, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_3Si$ $[M + H]^+$ 245.1573, found 245.1568.

**Bis(silyl ether) 40.** A solution of allylic alcohol **39** in $CH_2Cl_2$ (15 mL) was treated with imidazole (49 mg, 0.71 mmol, 1.5 equiv) and TBDPSCl (0.15 mL, 0.57 mmol, 1.2 equiv) at 0 ºC. The resulting solution was stirred for 12 h and then poured into $CH_2Cl_2$, washed with $H_2O$ and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain bis(silyl ether) derivative **40** (229 mg, quant.) as a colourless oil: $R_f$ = 0.89 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –9.45 (*c* 0.12, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70–7.65 (m, 4 H), 7.43–7.38 (m, 6 H), 5.80 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1 H), 5.19–5.13 (m, 1 H), 5.07 (dt, *J* = 10.6, 1.4 Hz, 1 H), 4.09 (t, *J* = 5.6 Hz, 1 H), 3.75 (dd, *J* = 11.9, 3.4 Hz, 1 H), 3.64 (dd, *J* = 11.9, 4.5 Hz, 1 H), 2.98 (dd, *J* = 5.5, 2.2 Hz, 1 H), 2.94–2.90 (m, 1 H), 1.16 (s, 9 H), 1.09 (s, 9 H), 0.90 (s, 3 H), 0.90 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.2, 134.8, 132.6, 130.3, 129.7, 127.9, 127.7, 127.5, 127.5, 74.9, 62.9, 58.8, 55.9, 27.0, 25.9, 20.7, 19.0, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{42}O_3Si_2$ $[M + H]^+$ 483.2751, found 483.2752.

**Epoxy Ether 41.** A solution of bis(silyl ether) **40** (229 mg, 0.48 mmol, 1.0 equiv) in $CH_2Cl_2$/MeOH mixture (4:1, 10 mL) was treated with CSA (11 mg, 0.05 mmol, 0.1 equiv) at 0 ºC. The reaction mixture was stirred at 0 ºC until depletion of starting material as judged by TLC (4.5 h). Then, the reaction was quenched by addition of $Et_3N$ (30 µL) and the resultant mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain epoxy ether **41** (262 mg, 75%) as a colourless oil: $R_f$ = 0.65 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = +28.6 (*c* 0.52, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.75–7.65 (m, 8 H), 7.47–7.34 (m, 12 H), 5.97–5.86

(m, 1 H), 5.86–5.76 (m, 1 H), 5.29–4.83 (m, 4 H), 4.57–4.48 (m, 1 H), 4.11 (t, *J* = 5.7 Hz, 1 H), 4.04–3.90 (m, 2 H), 3.90–3.76 (m, 2 H), 3.75–3.59 (m, 1 H), 3.57–3.32 (m, 1 H), 3.08 (dd, *J* = 5.6, 2.3 Hz, 1 H), 3.04–2.93 (m, 2 H), 2.65–2.45 (m, 1H), 1.12 (s, 9 H), 1.10 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 137.0, 137.0, 136.1, 136.1, 136.0, 135.9, 135.9, 135.8, 133.8, 133.7, 130.1, 129.9, 129.8, 129.7, 127.8, 127.8, 127.6, 127.5, 117.8, 116.7, 75.5, 74.8, 74.5, 73.5, 64.8, 61.2, 58.6, 55.8, 27.2, 26.9, 19.6, 19.4; HRMS (H-ESI) *m/z* calcd for $C_{44}H_{56}O_6Si_2$ $[M + Na]^+$ 759.3513, found 759.3506.

**Diepoxy Alcohol 42.** Silyl derivative **38** (212 mg, 0.57 mmol, 1.0 equiv) was dissolved in THF (10 mL) and to this solution was added TBAF (1.14 mL, 1.0 M in THF, 1.14 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1.15 h and, after this time, the reaction mixture was diluted with $Et_2O$ and washed with a saturated aqueous $NH_4Cl$ solution. The aqueous phase was then extracted with $Et_2O$ three times and the combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 30% EtOAc in hexanes) to obtain diepoxy alcohol **42** (127 mg, 87%) as a colourless oil: $R_f$ = 0.33 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –21.4 (*c* 0.24, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.96 (d, *J* = 12.8 Hz, 1 H), 3.69 (d, *J* = 11.8 Hz, 1 H), 3.27 (dd, *J* = 2.5, 1.9 Hz, 1 H), 3.25 (dd, *J* = 1.6, 1.1 Hz, 1 H), 3.17 (ddd, *J* = 7.3, 4.4, 2.0 Hz, 1 H), 3.13 (ddd, *J* = 8.5, 3.5, 1.3 Hz, 1 H), 3.12–3.06 (m, 1 H), 2.98 (dd, *J* = 3.6, 1.3 Hz, 1 H), 2.35 (bs, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 60.4, 59.8, 55.9, 55.8, 52.8, 3.5; HRMS (H-ESI) *m/z* calcd for $C_6H_9IO_3$ $[M + H]^+$ 256.9675, found 256.9675.

**Diepoxy Iodide 34. Olefination of Diepoxy Alcohol 42.** Diepoxy olefin **34** was prepared from diepoxy alcohol **42** (70 mg, 0.27 mmol, 1.0 equiv) by sequential treatments with $SO_3$·py and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **15**, to

obtain diepoxy alkene **34** (31 mg, 47% over two steps) whose physical and spectroscopic properties were identical to those obtained from **29**.

**α,β-Unsaturated Ester 45.** To a solution of ethyl-(*S*)-lactate **43** (3.2 mL, 27.94 mmol, 1.0 equiv) in $CH_2Cl_2$ (20 mL) was added TEA (8.30 mL, 61.47 mmol, 2.2 equiv), TBDPSCl (7.89 mL, 30.73 mmol, 1.1 equiv) and 4-DMAP (683 mg, 5.59 mmol, 0.2 equiv) at 0 ºC. The mixture was stirred for 12 h and then diluted with brine and the aqueous phase was extracted with $CH_2Cl_2$ three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain silyl derivative **44** (10 g, quant.) as a colourless oil which was used in the next step without further purification. A solution of silyl derivative **44** (10.0 g, 28.04 mmol, 1.0 equiv) in $CH_2Cl_2$ (60 mL) was cooled at -78 ºC and then treated with DIBAL-H (28 mL, 1.0 M in toluene, 28.04 mmol, 1.0 equiv). After 20 min, the reaction was quenched by dropwise addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous $Na^+/K^+$ tartrate solution and diluted with $CH_2Cl_2$. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The aqueous phase was then separated, the organic extract washed with water and brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting crude aldehyde (~28 mmol) was used in the next step without purification. A solution of tributyl(ethoxycarbonylmethylene)phosphonium bromide (11.0 g, 35.0 mmol, 1.25 equiv) in $CH_2Cl_2$ (40 mL) was washed twice with a 1.0 M aqueous NaOH solution (60 mL), then dried over $MgSO_4$ and diluted with toluene (40 mL). After removing $CH_2Cl_2$ under reduced pressure, the resulting solution was added to a stirred solution of the crude aldehyde and benzoic acid (682 mg, 5.60 mmol, 0.2 equiv) in toluene (100 mL) at 95 ºC. After 30 min at this temperature, the solvent was evaporated under reduced pressure and the resulting residue purified by flash column chromatography (silica gel, 10 % EtOAc in hexanes) to provide the corresponding α,β-unsaturated ester **45** (9.2 g, 86% over

two steps) as a colourless oil and whose spectroscopic and physical properties matched with those described in the literature:[42] $R_f$ = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +11.2 (*c* 0.89, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76–7.66 (m, 4 H), 7.48–7.37 (m, 6 H), 6.96 (ddd, *J* = 15.5, 4.5, 2.4 Hz, 1 H), 6.07 (ddd, *J* = 15.5, 2.6, 1.7 Hz, 1 H), 4.56–4.48 (m, 1 H), 4.24 (qdd, *J* = 7.0, 3.1, 1.0 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.18 (d, *J* = 6.5 Hz, 3 H), 1.15 (s, *J* = 2.2 Hz, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.8, 151.5, 135.9, 135.8, 134.1, 133.5, 129.1, 128.3, 127.7, 127.6, 119.2, 68.7, 60.3, 27.0, 23.4, 19.3, 14.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_3Si$ $[M + H]^+$ 383.2043, found 383.2040.

**Allylic Alcohol 46.** A solution of α,β-unsaturated ester **45** (9.0 g, 23.53 mmol, 1.0 equiv) in $CH_2Cl_2$ (50 mL) was cooled at -78 ºC and treated with DIBAL-H (70 mL, 1.0 M in toluene, 70.58 mmol, 3.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous $Na^+/K^+$ tartrate solution and diluted with $CH_2Cl_2$. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **46** (7.2 g, 90%) as a colourless oil and whose spectroscopic and physical properties matched with those described in the literature:[42] $R_f$ = 0.20 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.6 (*c* 0.43, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70–7.65 (m, 4 H), 7.46–7.33 (m, 6 H), 5.65 (dd, *J* = 15.4, 5.6 Hz, 1 H), 5.56 (dt, *J* = 15.4, 4.9 Hz, 1 H), 4.35 (p, *J* = 5.7 Hz, 1 H), 3.99 (d, *J* = 4.8 Hz, 2 H), 1.55 (bs, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.0, 135.9, 135.8, 134.5, 134.4, 129.6, 129.5, 127.8, 127.5, 127.4, 69.7, 63.1, 27.0, 24.2, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{21}H_{28}O_2Si$ $[M + H]^+$ 341.1937, found 341.1938.

**Epoxy Alcohol 47.** To a suspension of titanium tetraisopropoxide (2.4 mL, 8.22 mmol, 0.35 equiv) and 4Å molecular sieves (15.0 g) in $CH_2Cl_2$ (100 mL) was added (+)-L-DET (1.4 mL, 8.22 mmol, 0.35 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **46** (8.0 g, 23.49 mmol, 1.0 equiv) in $CH_2Cl_2$ (80 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (8.5 mL, 5.5 M solution in decane, 46.99 mmol, 2.0 equiv) at the same temperature. After 12 h at this temperature, the reaction mixture was quenched with $Me_2S$ (6.5 mL, 108 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy alcohol **47** (7.4 g, 88%) as a colourless oil: $R_f$ = 0.40 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –3.7 (*c* 0.9, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73–7.67 (m, 4 H), 7.45–7.37 (m, 6 H), 3.71 (dd, *J* = 12.8, 1.8 Hz, 1 H), 3.68–3.63 (m, 1 H), 3.41 (dd, *J* = 12.7, 4.3 Hz, 1 H), 2.91 (dd, *J* = 5.4, 1.9 Hz, 1 H), 2.71–2.67 (m, 1 H), 1.23 (d, *J* = 6.2 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 133.9, 133.8, 129.8, 129.7, 127.7, 127.6, 68.7, 61.3, 58.8, 57.4, 26.9, 20.9, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{21}H_{28}O_3Si$ $[M + H]^+$ 357.1886, found 357.1876.

**Epoxy Alkene 48.** Epoxy olefin **48** was prepared from epoxy alcohol **47** (4.6 g, 12.90 mmol, 1.0 equiv) by sequential treatments with $SO_3$·py and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **15**, to obtain epoxy alkene **48** (3.6 g, 80% over two steps) as a pale yellow oil: $R_f$ = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –11.7 (*c* 0.67, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.65 (m, 4 H), 7.43–7.36 (m, 6 H), 5.56–5.44 (m, 1 H), 5.32 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.21 (dd, *J* = 10.3, 1.5 Hz, 1 H), 3.60 (p, *J* = 6.1 Hz, 1 H), 2.90 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.81 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.97, 135.88, 135.2, 134.8,

134.0, 133.7, 129.8, 129.7, 127.7, 119.3, 69.1, 63.5, 57.7, 26.9, 20.9, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1935.

**Triepoxy Alcohol 49.** A solution of diepoxy olefin **29** (100 mg, 0.70 mmol, 1.0 equiv) and epoxy olefin **48** (744 mg, 2.11 mmol, 3.0 equiv) in degassed $CH_2Cl_2$ (7 mL) was reacted with Hoveyda-Grubbs 2nd generation catalyst (44 mg, 0.10 mmol, 0.10 equiv) according to the same procedure as described above for the synthesis of **10**, to afford triepoxy alcohol **49** (179 mg, 55%) as a colourless oil: $R_f$ = 0.56 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = +26.5 (*c* 0.39, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.64 (m, 4 H), 7.45–7.34 (m, 6 H), 5.60 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.45 (dd, *J* = 15.6, 7.4 Hz, 1 H), 3.76–3.67 (m, 2 H), 3.66–3.58 (m, 1 H), 3.34 (dd, *J* = 7.5, 1.9 Hz, 1 H), 3.19 (dt, *J* = 3.5, 2.3 Hz, 1 H), 3.11 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.93–2.89 (m, 2 H), 2.79 (dd, *J* = 5.6, 2.0 Hz, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.05 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 133.8, 133.7, 132.7, 130.2, 129.8, 129.7, 127.67, 127.6, 68.9, 63.9, 60.5, 57.9, 56.0, 55.8, 54.8, 53.1, 26.8, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2074, found 489.2073.

**Tosyl Derivative 50.** The tosylation of triepoxy alcohol **49** (65 mg, 0.14 mmol, 1.0 equiv) was achieved in exactly the same way as described above fot **30**, to obtain tosyl derivative **50** (105 mg, ~0.14 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (7.0 mg, ~0.009 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **50** (5.5 mg, 95%) as a colourless oil: $R_f$ = 0.83 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +20.6 (*c* 0.34, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82–7.78 (m, 2 H), 7.69–7.64 (m, 4 H), 7.44–7.40 (m, 2 H), 7.40–7.34 (m, 6 H), 5.61–5.52 (m, 1 H), 5.41 (dd, *J* = 15.7, 7.5 Hz, 1 H), 4.22 (dd, *J* = 11.7, 3.6 Hz, 1 H), 4.09 (dd, *J* = 11.6, 5.3 Hz, 1 H), 3.64–3.57 (m, 1 H), 3.32–3.27 (m, 1 H), 3.23–3.20 (m, 1 H), 3.00 (dd, *J* = 3.9, 2.0 Hz, 1 H), 2.91–2.86 (m, 2 H),

2.78 (dd, *J* = 5.6, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.05 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 145.3, 135.9, 135.8, 133.9, 133.8, 133.7, 133.0, 132.6, 130.0, 129.8, 129.7, 127.9, 127.7, 127.6, 68.9, 68.5, 63.8, 57.1, 55.9, 54.9, 53.8, 52.3, 26.9, 21.7, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2160.

**Iodide Derivative 51.** The iodination of crude tosyl derivative **50** (~98 mg, ~0.13 mmol, 1.0 equiv) was carried out according to the procedure described above for **31**, to afford iodide derivative **51** (97 mg, ~0.13 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (6.5 mg, ~0.009 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain pure iodide **51** (4.5 mg, 91%) as a colourless oil: $R_f$ = 0.66 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +12.1 (*c* 0.34 $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 5.59 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.43 (dd, *J* = 15.6, 7.9 Hz, 1 H), 3.63–3.57 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.7 Hz, 1 H), 3.28–3.24 (m, 2 H), 3.14–3.07 (m, 1 H), 2.98–2.91 (m, 2 H), 2.90 (dd, *J* = 7.3, 2.1 Hz, 1 H), 2.79 (dd, *J* = 5.6, 2.0 Hz, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 133.8, 133.7, 132.9, 130.0, 129.9, 129.8, 127.7, 127.6, 68.9, 63.9, 59.4, 57.3, 55.9, 55.7, 54.8, 26.9, 20.8, 19.2, 3.1; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + Na]^+$ 599.1091, found 599.1090.

**Allylic Alcohol 52.** A solution of diepoxy iodide **51** (~91 mg, ~0.12 mmol, 1.0 equiv) in THF (10 mL) was reacted with *n*-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **32**, to afford, after similar processing, allylic alcohol **52** (50 mg, 91% over 3 steps): $R_f$ = 0.50 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +18.9 (*c* 0.23, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.64 (m, 4 H), 7.42–7.34 (m, 6 H), 5.96 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.57 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.45 (dd, *J* = 12.3, 4.4 Hz, 1 H), 5.29 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.15–4.09 (m, 1 H),

3.60 (p, *J* = 6.1 Hz, 1 H), 3.38 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.97 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.90 (dd, *J* = 7.2, 1.9 Hz, 1 H), 2.80 (dd, *J* = 5.7, 2.0 Hz, 1 H), 2.05 (bs, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.2, 135.9, 135.8, 133.8, 133.7, 132.6, 130.6, 129.8, 129.7, 127.7, 127.6, 117.0, 71.6, 69.0, 63.8, 62.4, 56.2, 55.1, 26.9, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2315.

**10-*epi*-Depudecin (53).** Silyl derivative **52** (16 mg, 0.04 mmol, 1.0 equiv) was desilylated by the action of TBAF (0.04 mL, 1.0 M in THF, 0.04 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**1**) to afford 10-*epi*-depudecin (**53**) (6.0 mg, 85%) as a colourless oil: $R_f$ = 0.52 (silica gel, EtOAc); $[\alpha]^{25}_D$= +33.3 (*c* 0.9, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.73–5.70 (m, 2 H), 5.39 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.01 (dd, *J* = 4.4, 1.8 Hz, 1 H), 3.48–3.45 (m, 1 H), 3.44–3.41 (m, 1 H), 3.01 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.94 (dd, *J* = 3.0, 2.2 Hz, 1 H), 1.98 (d, *J* = 6.5 Hz, 1 H), 1.87 (bs, 1 H), 1.27 (d, *J* = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.1, 132.2, 131.4, 117.1, 71.5, 64.6, 63.5, 62.4, 54.9, 53.5, 18.7; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1129.

**Diepoxy Amide *ent*-21.** Epoxy alcohol *ent*-**20**[44] (133 mg, 0.62 mmol 1.0 equiv) was dissolved in a $CH_2Cl_2$/DMSO (1:1) mixture (2.5 mL) and cooled at 0ºC. At this temperature, $Et_3N$ (0.25 mL, 1.83 mmol, 3.0 equiv) was added followed by $SO_3$·Pyr (175 mg, 1.08 mmol, 1.8 equiv). The reaction mixture was allowed to reach 25 ºC and, after 5 h, was quenched by addition of a buffer solution (pH = 7) and diluted with $Et_2O$. The aqueous phase was extracted with $Et_2O$ and the combined organic extracts were washed with water and brine, then dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a suspension of sulfonium salt *ent*-**12** (221 mg, 0.71 mmol, 1.1 equiv) in *t*-BuOH (8.0 mL) was added a 5.0 M aqueous

NaOH solution (0.13 mL, 0.63 mmol, 1.0 equiv) at 25 ºC. After 1 h at this temperature, a solution of crude aldehyde in *t*-BuOH (2.1 mL) was added and the resulting reaction mixture was stirred overnight. The crude mixture was then diluted with $CH_2Cl_2$ and $H_2O$ and, after separation of both phases, the aqueous layer was extracted with $CH_2Cl_2$ three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy amide *ent*-**21** (179 mg, 68% over 2 steps) as a pale yellow oil: $R_f$ = 0.21 (Silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +26.7 (*c* 0.40, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.27 (ddd, *J* = 8.4, 4.7, 3.3 Hz, 1 H), 3.96 (ddd, *J* = 9.2, 5.2, 1.2 Hz, 1 H), 3.88–3.86 (m, 1 H), 3.85 (d, *J* = 2.4 Hz, 1 H), 3.68 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.54 (d, *J* = 2.0 Hz, 1 H), 3.29 (dd, *J* = 3.4, 2.0 Hz, 1 H), 3.07 (dq, *J* = 3.5, 2.2 Hz, 2 H), 2.58–2.49 (m, 1 H), 2.47–2.39 (m, 1 H), 2.07 (s, 3 H), 1.80–1.73 (m, 1 H), 1.58 (s, 3 H), 1.47 (s, 3 H), 0.83 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.9, 95.9, 67.0, 61.6, 56.3, 55.9, 55.5, 51.7, 51.2, 34.4, 30.6, 26.2, 25.6, 22.9, 18.3, 15.7, –3.6, –5.4; HRMS (H-ESI) *m/e* calcd for $C_{20}H_{37}NO_5SSi$ $[M + H]^+$ 432.2240, found 432.2242.

**Diepoxy Alkene *ent*-16.** Diepoxy olefin *ent*-**16** (67 mg, 52% over two steps) was prepared from epoxy amide *ent*-**21** (190 mg, 0.34 mmol, 1.0 equiv) by sequential treatments with Red-Al and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **16**. **[*ent*-16]:** colorless oil; $R_f$ = 0.87 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +29.9 (*c* 0.45, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.63–5.47 (m, 2 H), 5.33–5.29 (m, 1 H), 3.87 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.74 (dd, *J* = 12.2, 4.1 Hz, 1 H), 3.35 (dd, *J* = 7.1, 2.1 Hz, 1 H), 3.10 (ddd, *J* = 4.0, 2.8, 2.2 Hz, 1 H), 2.99 (dd, *J* = 4.4, 2.1 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.1 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.4, 120.2, 62.1, 57.9,

56.0, 55.9, 53.3, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{13}H_{24}O_3Si$ $[M + H]^+$ 257.1573, found 257.1576.

**Diepoxy alcohol *ent*-29.** Diepoxy alcohol *ent*-**29** (33 mg, 85%) was prepared from silyl ether *ent*-**16** (67 mg, 0.26 mmol, 1.0 equiv) by treatment with TBAF according to the same procedure described above for the preparation of **29**. **[*ent*-29]:** colourless oil; $R_f$ = 0.32 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 23.3 (*c* 0.33, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.47–5.37 (m, 2 H), 5.24–5.18 (m, 1 H), 3.79 (ddd, *J* = 11.4, 9.0, 2.5 Hz, 1 H), 3.53 (dd, *J* = 12.9, 4.3 Hz, 1 H), 3.29–3.25 (m, 1 H), 3.05 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95–2.90 (m, 1 H), 2.81 (dd, *J* = 4.8, 2.1 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.2, 120.4, 60.7, 57.9, 56.0, 55.9, 53.5; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_3$ $[M + H]^+$ 143.0708, found 143.0712.

**Epoxy Alkene *ent*-28.** Epoxy olefin *ent*-**28** was prepared from epoxy alcohol *ent*-**27** (3.8 g, 10.66 mmol, 1.0 equiv) by sequential treatments with $SO_3$·py and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **15**, to obtain epoxy alkene *ent*-**28** (3.3 g, 87% over two steps) whose spectroscopic and physical properties were identical to epoxy alkene **28**, except for its specific rotation: $[\alpha]^{25}_D$ = –11.5 (*c* 0.45, $CH_2Cl_2$); HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1936.

**Triepoxy Alcohol *ent*-10.** A solution of diepoxy olefin *ent*-**29** (33 mg, 0.23 mmol, 1.0 equiv) and epoxy olefin *ent*-**28** (245 mg, 0.70 mmol, 3.0 equiv) in degassed $CH_2Cl_2$ (7 mL) was reacted with Hoveyda-Grubbs 2$^{nd}$ generation catalyst (14 mg, 0.03 mmol, 0.10 equiv) according to the same procedure as described above for the synthesis of **10**, to afford triepoxy alcohol *ent*-**10** (53 mg, 52%) as a colourless oil: $R_f$ = 0.56 (silica gel, 60% EtOAc in hexanes); $R_f$ = 0.34 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +28.7 (*c* 0.41, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72–7.65 (m, 4 H), 7.46–7.34 (m, 6 H), 5.70 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.58

(dd, *J* = 15.7, 7.3 Hz, 1 H), 3.97 (dd, *J* = 12.9, 2.3 Hz, 1 H), 3.76–3.68 (m, 2 H), 3.37 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.20 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.19– 3.17 (m, 1 H), 3.10 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 2.93 (dd, *J* = 4.3, 2.1 Hz, 1 H), 1.54–1.49 (bs), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.9, 135.8, 134.2, 133.6, 132.8, 130.5, 129.7, 129.6, 127.6, 127.5, 69.7, 64.6, 60.5, 57.9, 55.8, 54.8, 54.6, 53.0, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2073, found 489.2066.

**Tosyl Derivative *ent*-30.** The tosylation of triepoxy alcohol *ent*-**10** (19 mg, 0.04 mmol, 1.0 equiv) was achieved in exactly the same way as described above fot **30**, to obtain tosyl derivative *ent*-**30** (35 mg, ~0.04 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (2.5 mg, ~0.0029 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain tosyl derivative *ent*-**30** (1.7 mg, 94%) as a colourless oil: $R_f$ = 0.74 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +11.3 (*c* 0.20, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82–7.77 (m, 2 H), 7.72–7.66 (m, 4 H), 7.45–7.34 (m, 8 H), 5.68 (dd, *J* = 15.6, 7.3 Hz, 1 H), 5.54 (dd, *J* = 15.7, 7.5 Hz, 1 H), 4.21 (dd, *J* = 11.7, 3.7 Hz, 1 H), 4.08 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.76–3.69 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.8 Hz, 1 H), 3.23–3.20 (m, 1 H), 3.19 (dd, *J* = 7.2, 2.1 Hz, 1 H), 2.98 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 2.89 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 145.3, 135.9, 135.8, 134.2, 133.6, 133.1, 132.6, 130.2, 130.0, 129.7, 129.6, 127.9, 127.6, 127.5, 69.7, 68.5, 64.6, 57.1, 54.8, 54.6, 53.8, 52.3, 26.9, 26.8, 21.7, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2153.

**Iodide Derivative *ent*-31.** The iodination of crude tosyl derivative *ent*-**30** (~32 mg, ~0.037 mmol, 1.0 equiv) was carried out according to the procedure described above for **31**, to afford iodide derivative *ent*-**31** (30 mg, ~0.037 mmol), which did not require further purification for

the next step. For analytical purposes, a sample of this crude (3.0 mg, ~0.0037 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain pure iodide *ent*-**31** (2.0 mg, 95%) as a colourless oil: $R_f$ = 0.83 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +11.1 (*c* 0. 30 $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72–7.66 (m, 4 H), 7.46–7.34 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.56 (dd, *J* = 15.7, 7.4 Hz, 1 H), 3.78–3.69 (m, 1 H), 3.35 (d, *J* = 7.2 Hz, 1 H), 3.28–3.23 (m, 2 H), 3.20 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.14–3.08 (m, 1 H), 2.97–2.94 (m, 3 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 135.88, 135.84, 134.19, 133.64, 132.96, 130.31, 129.69, 129.67, 127.60, 127.6, 69.7, 64.6, 59.4, 57.3, 55.7, 54.7, 54.6, 26.9, 19.9, 19.3, 3.1; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + H]^+$ 577.1271, found 577.1259.

**Allylic Alcohol *ent*-32.** A solution of crude iodide *ent*-**31** (~24 mg, ~0.033 mmol, 1.0 equiv) in THF (4 mL) was reacted with *n*-BuLi (41.0 µL, 1.6 M in hexane, 0.066 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **32**, to afford, after similar processing, allylic alcohol *ent*-**32** (13 mg, 89% over 3 steps) as a colourless oil: $R_f$ = 0.48 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +16.9 (*c* 0.19, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71– 7.66 (m, 4 H), 7.46–7.34 (m, 6 H), 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.67 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.59 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.43–5.37 (m, 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.17–4.10 (m, 1 H), 3.76– 3.70 (m, 1 H), 3.40 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.20 (dd, *J* = 7.0, 2.1 Hz, 1 H), 2.99 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.88 (d, *J* = 6.6 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.9, 135.8, 133.1, 133.0, 132.6, 130.9, 129.7, 129.6, 127.6, 127.5, 117.0, 71.5, 69.7, 64.5, 62.4, 54.9, 54.7, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2315.

**(+)-Depudecin (*ent*-1).** Silyl derivative *ent*-**32** (8 mg, 0.02 mmol, 1.0 equiv) was desilylated by the action of TBAF (0.02 mL, 1.0 M in THF, 0.02 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**1**) to afford (+)-depudecin (*ent*-**1**) (3.0 mg, 88%) as a colourless oil: $R_f$ = 0.50 (silica gel, EtOAc); $[\alpha]^{25}_D$= +35.6 (*c* 0.38, $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.95 (ddd, *J* = 17.2, 10.6, 5.5 Hz, 1 H), 5.73–5.71 (m, 2 H), 5.41 (dt, *J* = 17.3, 1.3 Hz, 1 H), 5.29 (dt, *J* = 10.6, 1.2 Hz, 1 H), 4.15 (d, *J* = 5.4 Hz, 1 H), 3.79–3.74 (m, 1 H), 3.46–3.44 (m, 1 H), 3.41–3.39 (m, 1 H), 3.03 (dd, *J* = 4.2, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.5, 2.2 Hz, 1 H), 1.90 (d, *J* = 6.4 Hz, 1 H), 1.77 (d, *J* = 6.0 Hz, 1 H), 1.32 (d, *J* = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 136.1, 132.0, 131.5, 117.1, 71.5, 66.9, 64.1, 62.4, 55.3, 54.9, 20.0; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1118.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

$^1$H and $^{13}$C NMR spectra for all new compounds.

## AUTHOR INFORMATION

### Corresponding Author

* E-mail: frsarabia@uma.es

### Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

### Notes

The authors declare no competing financial interest.

## Dedication

Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

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